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THE STORY OF SHIPYARD EYE*

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The title of this lecture sounds rather mysterious, suggesting the adventures of a one-eyed pirate who sabotages shipyards. In fact, this account does have much in common with a detective story: it is replete with mystery, mistaken identity, a missing phial of poison, and the final dénouement in which the hero of the beginning of the story turns out to be the villain.

My story begins 70 years ago, in 1889, when several Austrian ophthalmologists (Fuchs, 1889) described a new disease entity under various names. The illness consisted of an acute conjunctivitis with extreme oedema of the conjunctiva, pain, photophobia, and lacrimation, followed by superficial erosions of the cornea, and finally by deeper, opaque subepithelial corneal infiltrates located just beneath Bowman's membrane. These unique opacities were round, located mainly in the centre of the cornea, and they persisted for up to two years. If the opacities were large or numerous enough they seriously impaired vision. Systemic manifestations of illness were lacking.

In the next 40 years many reports appeared in the medical literature indicating that this illness was world-wide. Epidemics involving thousands of persons were described in Asia and sporadic cases occurred in European countries. Controversies arose among ophthalmologists regarding the possible identity of similar disease pictures, and many suggestions were made concerning the possible aetiology of the illness. However, bacteriological studies remained inconclusive. Wright (1930), who observed some 3,500 cases in Madras, suggested a viral aetiology and transmitted the typical disease to volunteers by means of filtered conjunctival washings.

During the summer of 1941 a very large outbreak (more than 10,000 cases) occurred in Hawaii, at the Naval shipyards of Pearl Harbour. Soon thereafter the illness made its appearance on the West Coast of the United States. Several thousand cases were diagnosed, most of them workers in shipyards. Members of their families and other close contacts were rarely affected. Hogan and Crawford (1942) studied 125 patients in detail and coined the name "epidemic kerato-conjunctivitis," abbreviated as E.K.C. However, the popular name "shipyard eye" was attached to the disease, and this name persisted even when the illness spread to other industries across North America in 1941–2, seriously hampering war production. By then exhaustive studies had ruled out a bacterial aetiology, and the apparent infectious nature of the illness made a search for causative viruses mandatory.

Search for a Virus

Techniques for virus isolation were well advanced at that time. Perhaps the most intensive search for a specific virus was made by Dr. Murray Sanders and his associates. They inoculated material from infected eyes into embryonic mouse brain in a Maitland-type tissue culture. After several passages in that medium the intracerebral inoculation of mice resulted in neurological symptoms and death. The virus was stated to be also fatal for rabbits and some monkeys, and to be neutralized by sera from several E.K.C. patients, but not by antisera to the viruses of herpes simplex, lymphocytic choriomeningitis, or Theiler's mouse encephalomyelitis. The inoculation of one volunteer resulted in acute conjunctivitis but no keratitis. The publications by Dr. Sanders and his group appeared in 1943 (Sanders and Alexander, 1943; Sanders *et al.*, 1943). Dr. Sanders went off to war, and the virus gained admission into textbooks as the "virus of epidemic keratoconjunctivitis."

The Missing Phial

We now come to the missing phial of poison. After the second world war several virologists wanted to examine the "virus of E.K.C." They searched for a strain of Sanders's agent in various laboratories, refrigerators, and dry ice cabinets, but alas—the virus had disappeared. Only a single tube labelled "Virus of E.K.C.," perhaps originating in Dr. Sanders's laboratory, could be discovered. It was carefully examined by Ruchman (1951) and by Cheever (1957), who noted to their dismay that it was actually a strain of St. Louis encephalitis virus. Sera from patients who contracted E.K.C. in 1951 contained no antibodies to this agent (Ormsby and Fowle, 1954). Competent virologists failed to recover a virus from the 1951 outbreaks of E.K.C. by Sanders's technique, although latent mouse viruses were occasionally activated in the course of mouse passage. To confound the confusion there were scattered reports from several countries describing the "isolation of the virus of E.K.C." It was difficult to accept these reports, because the descriptions of no two of these viruses resembled each other, and the agents appeared to be too fragile to permit their transportation from the discoverer to other investigators. At that point our group felt that perhaps it would be best to discard the accumulation of myth, fiction, and hearsay and take a new look at the aetiology of E.K.C.

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In December, 1954, a seaman (Trim) came to our clinic at the University of California in San Francisco suffering from intensely painful red eyes for 12 days. The illness had started on board ship several days after his departure from an Oriental port, with an "inflammation" in the right eye, and had spread to the left eye about four days later. On examination he exhibited a very severe conjunctivitis with pseudomembrane formation and enlarged pre-auricular nodes. A few days later he developed the typical subepithelial corneal opacities of E.K.C. (Fig. 1). The nurse who took care of him also contracted E.K.C. 10 days after her initial contact with the patient, and eventually developed typical opacities (Fig. 2).

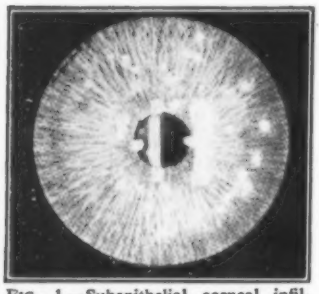

FIG. 1.—Subepithelial corneal infiltrates in patient Trim 99 days after onset of eye symptoms (artist's drawing). Reproduced, by permission, from *Amer. J. Ophthal.*, 1955, **40**, 203.

FIG. 2.—Subepithelial corneal infiltrates (clinical photograph) typical of epidemic keratoconjunctivitis in nurse of patient Trim. Reproduced, by permission, from *Amer. J. Ophthal.*, 1955, **40**, 203.

Adenovirus Type 8

Scrapings were taken from the conjunctivae of our patient (Trim) and inoculated into tissue cultures of strain HeLa cells. After an unusually protracted period of incubation these cultures yielded a cytopathogenic virus, subsequently established as the prototype of adenovirus type 8 (Jawetz *et al.*, 1955). Up to the present time some 100 strains of this agent have been isolated all over the world, all from the eye, and with rare exceptions all from typical cases of E.K.C. Acute and convalescent serum specimens obtained since 1952 from patients with E.K.C. regularly exhibited a rise in neutralizing antibodies for adenovirus type 8.

A serological survey was conducted in several countries where E.K.C. had recently occurred. Among 132 patients carrying the diagnosis of E.K.C. 80% had antibodies to adenovirus type 8 in a serum dilution of 1:10 or greater. Among 106 individuals of similar age and place of residence who had no history of clinical E.K.C., only 8.6% had such antibodies. These findings pointed strongly to a constant association between adenovirus type 8 and typical E.K.C. (Hanna *et al.*, 1957). It was, of course, desirable to establish a similar serological pattern for patients who had contracted E.K.C. prior to 1952. Regrettably, properly stored serum obtained in the 1940s from patients with active clinical E.K.C. has not been available. Regrettably, also, the titre of neutralizing antibodies to adenovirus type 8 declines rapidly in man, so that diagnostic levels are not usually encountered more than two years after the onset of clinical E.K.C. (Jawetz *et al.*, 1956). Thus we have been unable to diagnose by retrospective serology the aetiological agent involved in the E.K.C. epidemics of the early 1940s.

Final proof for the aetiological role of adenovirus type 8 in E.K.C. came from the inoculation of volunteers. Mitsui *et al.* (1957) regularly produced E.K.C. by the instillation of adenovirus type 8 grown in tissue culture into the eyes of volunteers, provided they possessed no specific antibody to that virus. Conversely, neutralizing antibody concentrations of 1:20 or greater in the serum protected volunteers against disease after experimental inoculation. Such antibody was, at times, present as the result of clinical or subclinical infection in the past, or it could be induced artificially by repeated subcutaneous injections of active adenovirus grown in tissue culture. Specific neutralizing antibodies protected against challenge infection with either infectious material from fresh cases of E.K.C. or with laboratory-grown adenovirus type 8 (Mitsui *et al.*, 1959).

Some Peculiar Properties

In laboratory studies of several strains adenovirus type 8 exhibited some peculiar properties which set it apart from other types of the adenovirus group. When grown in a variety of cell strains in tissue culture the yield of infective virus was invariably very low, never exceeding 300 tissue culture infective doses (TCD50). Extracellular virus was extremely stable, persisting at room temperature for weeks. Only a portion of the inoculated virus was adsorbed on to cell sheets, yet there was no evidence to suggest that certain cells were much more resistant than others. In spite of the low yield of infective virus the total antigenic mass in such tissue cultures was high, when estimated as complement-fixing antigen.

While this test admittedly detects mainly a soluble antigen, distinct from the infective particle, it seemed probable that it reflected the total amount of virus synthesis in culture. If this assumption is correct most of the virus produced in culture is non-infective. The ratio of infective virus to complement-fixing antigen in cultures of adenovirus type 8 (200 TCD50/ml. and 160–640 units antigen/ml.) was quite different from that usually encountered with type 4 (3,000 TCD/ml. and 80–320 units antigen/ml.). Thus it was reasonable to assume that infective virus constituted only a minute fraction of the total antigenic mass produced in the course of viral growth. The question naturally arose whether the non-infective antigenic material, the postulated non-infective virus, might account for some of the biological peculiarities of adenovirus type 8.

It is quite possible that non-infective antigen interferes with the adsorption of infective virus on to susceptible cells, or with infective virus production after adsorption. This might account for the uniformly low infective titres of type 8 encountered in many laboratories. If non-infective antigen were capable of combining with specific antibody it might effectively compete with infective virus for available antibody molecules in virus–serum mixtures. This might explain the extremely narrow range of virus concentrations—usually only threefold to tenfold—which can be employed in serum-neutralization tests (Jawetz *et al.*, 1958). This odd behaviour of adenovirus type 8 in the laboratory makes one wonder whether similar features might be exhibited in human infections and might, perhaps, account for the curious epidemiological pattern of E.K.C.

The Diverse Epidemiology of E.K.C.

Several puzzling aspects of the epidemiology of E.K.C. have been noted in the past (Thygeson, 1948). In most

outbreaks in the Western world, particularly in the United States, Canada, and Britain, the disease was sharply limited to adult workers in certain industries—for example, shipyards—with only negligible spread to members of their immediate families, in spite of close and protracted contact. Other outbreaks centred around hospitals where eye surgery was performed, or offices of ophthalmologists. There appeared to be virtually no subclinical infection in the population at large, and E.K.C. was not seen in children. Neutralizing antibodies were encountered in only 4–5% of persons who lived in the area of a recent epidemic but had not themselves suffered from the disease.

In Oriental countries, particularly Japan, the epidemiological pattern seemed to be quite different (Tanaka, 1957). E.K.C. was not principally an industrial disease. As pointed out by Mitsui *et al.* (1955), children were commonly infected. They developed a systemic illness with fever, respiratory or gastro-intestinal symptoms, and a pseudomembranous conjunctivitis, but no keratitis. Sporadic cases in adults often occurred in families with infected children. Subclinical or mild infection appeared to be relatively common. Between 25 and 33% of the general population had a significant antibody titre to adenovirus type 8. How can one explain such different epidemiological behaviour of the same virus in different parts of the world ?

The Virus in Action

We had an opportunity to get a glimpse of this virus in action when a member of our group contracted an accidental infection with adenovirus type 8 in the laboratory.

This 41-year-old technician and five other persons had handled adenovirus type 8 in routine laboratory procedures for from two to four years without ever developing clinical or serological evidence of infection. The accidental contamination probably occurred while she injected, repeatedly, large volumes of infective tissue culture fluids into rabbits. Soon thereafter she had a severe and entirely typical attack of E.K.C., involving both eyes and leading to the unmistakable subepithelial corneal opacities. She was closely observed clinically during the entire course of illness, and conjunctival scrapings for virus isolation as well as serum specimens were obtained frequently. All her close contacts were also examined. The results of these observations were remarkable. In spite of the extremely pronounced inflammatory response and chemosis, persisting for several days, only minute quantities of infective adenovirus type 8 were recovered from the patient's eyes. Only on the first day of each eye's involvement could more than three tissue culture infective doses be collected. During the remainder of the two weeks of acute eye involvement virus was isolated with great difficulty, requiring one or more blind passages in tissue culture.

Thus it became evident that in this patient, as in tissue cultures, very little infective virus was released and hence she did not transmit the agent to others. Indeed, her husband, four children aged 7–12, and several close associates remained uninfected both clinically and serologically, although she used no aseptic precautions whatever during the earliest days of profuse lacrimation when the largest amount of infective virus was recovered. Because of the small quantity of material in conjunctival scrapings it was unfortunately not possible to assay for non-infective antigen. However, this accidental infection suggested that the amount of infective virus produced in the adult eye was insufficient for spontaneous transmission of E.K.C., and that special circumstances were required to produce infection at all. Among these, direct inoculation of the eye by fingers, instruments, or solutions, and a relatively concentrated inoculum appeared important. The eye is probably the only portal of entry which permits the establishment of symptomatic infection by adenovirus type 8 in adults. Subcutaneous injection of the highest available concentration of infective virus (as undiluted tissue culture fluid) into volunteers failed to induce clinical disease (Mitsui *et al.*, 1959).

A Possible Explanation

All these threads of evidence may now be woven into the following tentative explanation for the diverse epidemiology of E.K.C.

The adult is not highly susceptible to adenovirus infection, the eye being the sole portal of entry and the principal susceptible tissue. Infection is likely to occur only if a large inoculum is placed direct into the eye. Infection of the adult yields very small amounts of infective virus, so that spontaneous transmission is improbable. Spread from one adult to another must therefore depend on direct transfer of virus from one eye to another. The individual most likely to accomplish such a transfer appears to be a nurse or physician engaged in examining the eye. The extreme stability of extracellular adenovirus aids the persistence of infective virus in ophthalmic solution or on instruments. Thus E.K.C. in the Western world appears to be largely an iatrogenic disease. Because of the low spontaneous transmissibility of the infection, antibodies and immunity are infrequent in the general population. Thus virtually all persons exposed to the manipulations of an eye physician are susceptible to infection, and should he disseminate virus an explosive outbreak ensues. The shipyard, with its chemical and mechanical irritants, brings many workers to the dispensary, where doctor or nurse may inoculate them with adenovirus type 8. Epidemics of " shipyard eye " continue to occur. This pattern appears applicable in the United States, Great Britain, and Canada, and is well supported by factual evidence.

For Oriental countries such as Japan an alternative epidemiological pattern may be proposed. Small children appear to be relatively susceptible to adenovirus infection. They may commonly develop a systemic illness with only minor involvement of the eye. It is possible—but needs to be established—that the yield of infective virus from children is much higher than from adults. Thus a child might spread the agent effectively to other children (possibly through respiratory or gastro-intestinal excretions) and to adults. When childhood infection is prevalent a mechanism exists for the endemic maintenance of the infection in the population. In such circumstances the dispensary may play only a minor part in the spread of the disease. While much of this hypothesis is entirely speculative, some facts in its support are established now. Childhood infection is common in Japan ; children are commonly the first members of the family group to be infected (Mitsui and Jawetz, 1957) ; between one-fourth and one-third of the population have antibodies to adenovirus type 8, suggesting a high endemic level of infection. The

systemic nature of the childhood infection and its prevalence suggest that it can be acquired spontaneously by routes other than eye-to-eye transmission. However, we lack information about the quantity and route of virus excretion in the child and the precise nature of its transmission.

Conclusion

Thus I have come to the end of my story of shipyard eye. At present adenovirus type 8 unquestionably causes epidemic keratoconjunctivitis, and it may well be the sole cause of this disease in its typical form. Thus it is proper henceforth to support the clinical impression of E.K.C. by laboratory evidence of infection with adenovirus type 8—either by virus isolation or by the demonstration of a rise in specific neutralizing antibody titre. The mythical "virus of epidemic keratoconjunctivitis" or "Sanders virus" of textbooks may be discarded—the poison phial is lost for ever. Finally—in North America and Great Britain at least—the hero of the beginning of the story, the eye physician, is the villain at the end. It is he who spreads the virus among his patients in shipyard, office, and hospital, and who is responsible for outbreaks of the disease in the Western world.

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"The previous year was disappointing enough, but the year under review has been the most frustrating in the 21 years' history of the Nuffield Department of Anaesthetics. Any scientific investigation, and much of the routine work, in the 'temporary' accommodation of this, the first of the Nuffield Medical Departments, has been made almost impossible by the distractions of noise and dust from the contiguous new buildings which are being erected in accordance with the policy of catering for undergraduate clinical teaching. This miserable state of affairs was verified by visits of three of the Nuffield Trustees and the then Chairman of the Board of Governors of the United Oxford Hospitals. In the department there are posts for four graduate assistants, for which hitherto there has always been keen competition. A year ago all four assistants tendered their resignations. Dr. Epstein was persuaded to continue, but even at the time of writing this report conditions have not improved sufficiently to attract inquiries from suitable candidates for the other posts. Owing to the fact that there was no suitable accommodation, the visit to Oxford of 20 Continental anaesthetists organized by the British Council had to be restricted to an inspection of the respiration unit—and a sight-seeing tour of the city."—*Oxford University Gazette*, March 6, 1959.

DIURETIC EFFECT OF STEROID THERAPY IN OBSTINATE HEART FAILURE

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"A creaking door hangs longest."—ANON.

Clinical experience in the relief of heart failure has evolved an effective therapeutic routine, the roots of which are buried in herbal folklore, its branches growing into the realms of biochemistry and endocrinology. The beneficial effect of bed rest, digitalis administration, diuretic therapy, and a low-salt regimen have proved the efficacy of this routine, but in oft-repeated or long-continued congestive heart failure this treatment may become ineffective. The clinician is dispossessed of his traditional remedies and the patient succumbs with unrelenting dropsy.

The inadequacy of treatment in late-stage heart failure has become apparent with increasing frequency since antibiotics, by reducing the hazard of intercurrent infection, have prolonged the lives of cardiac patients, allowing heart failure to continue its variable course and eventually to persist as a permanent state. That intractable heart failure is capable of responding to routine therapy following the administration of prednisone has been shown by Muller *et al.* (1956a) and by Gutner *et al.* (1957). Their results, however, were not uniformly successful.

It is the purpose of this paper to describe a rationale for the success of prednisolone therapy in patients with obstinate heart failure.

Heart Failure

When the heart fails, the inability of the cardiac output to satisfy the metabolic demands of the tissues (Altschule, 1938) initiates circulatory adjustments attempting to correct this deficiency. The cardiac output is augmented by a compensatory increase in circulating blood volume which results from an independent variation of renal excretion of sodium and water, at times even at the expense of the tissue fluid tonicity (McCance, 1936; Leaf *et al.*, 1953; Weston *et al.*, 1953). Initially a primary retention of sodium occurs, with water retention a secondary phenomenon. Since sodium predominates in the extracellular space, fluid accumulates in this compartment, thereby increasing plasma volume (Gibson and Evans, 1937; Berson, 1954), venous pressure, and interstitial fluid volume, manifested as oedema. The haemodynamic principles of the "backward failure" hypothesis (Hope, 1832) largely determine the distribution of this excess fluid in either the peripheral or the pulmonary circulation. The ultimate clinical picture is also influenced by such factors as the character of the heart lesion, salt and water intake, physical activity, local tissue metabolism, and therapy.

These principles, however, cannot be applied to all patients with heart failure. Hollander and Judson

(1956) have shown that sodium retention occurs only in patients with systemic congestion and significant elevation of right ventricular and diastolic pressure, whereas most patients with pulmonary congestion but normal venous pressure can excrete loads of sodium and water. Furthermore, salt deficiency can be induced in patients with chronic congestive heart failure without reducing their oedema and, indeed, on occasions, whilst oedema is accumulating. Clearly, persistent oedema in these patients must be due to primary water retention, occurring, moreover, despite hypotonicity of tissue fluid.

Factors Regulating Salt and Water Retention in Congestive Heart Failure

The relative importance of the factors influencing renal tubular function, with respect to salt and water excretion, is difficult to assess. Those of major importance and capable of independent variation include (1) alterations in renal haemodynamics, (2) adrenocortical function, and (3) posterior pituitary activity.

1. Alterations in Renal Haemodynamics

A diminished glomerular filtration rate has been shown to enhance tubular reabsorption of sodium and water (Hanenson *et al.*, 1953). Greatly reduced renal plasma flows and reduced glomerular filtration rates have been reported in patients with chronic congestive heart failure (Merrill, 1946; Mokotoff *et al.*, 1946).

2. Adrenocortical Function

Since the isolation of a potent sodium-retaining factor from adrenal venous blood and its later identification as aldosterone (Simpson and Tait, 1952; Simpson *et al.*, 1952, 1954) this adrenocortical hormone has been obtained in crystalline form from patients with nephrosis (Luetscher *et al.*, 1954) and congestive heart failure (Luetscher *et al.*, 1956). Further studies on oedematous patients with renal, hepatic, and cardiac disease have shown that sodium retention in these subjects is associated with an increased excretion of aldosterone (Liddle *et al.*, 1955; Duncan *et al.*, 1956; Muller *et al.*, 1956b, 1956d; Wolff *et al.*, 1957a, 1957b; Thorn et al., 1957).

Aldosterone encourages salt retention by increasing tubular reabsorption of sodium and chloride; it also stimulates distal tubular exchange of potassium, ammonium, and hydrogen ions for sodium ions in the tubular luminal fluid.

As Greep and Deane (1947) postulated, there is evidence that some degree of adrenal autonomy exists in the production of aldosterone. Thorn *et al.* (1957) found that the baseline secretion of aldosterone was not as intimately dependent upon corticotrophin as that of adrenal hydroxysteroids and ketosteroids, and its secretion in response to corticotrophin administration was variable, in contrast with the consistent stimulation of glucocorticoids under similar conditions.

Although baseline adrenal aldosterone secretion appears to be independent of anterior pituitary function to a large extent, administration of corticotrophin to patients maintained on a low-sodium diet is accompanied by a rise in urinary aldosterone excretion (Duncan *et al.*, 1956; Muller *et al.*, 1956c; Thorn *et al.*, 1957).

Aldosterone secretion is influenced by the volume of the body fluids (Liddle *et al.*, 1955). Thus increased aldosterone activity follows reduction of extracellular volume by bleeding, salt depletion, drainage of ascites, and diuresis (Bartter *et al.*, 1956; Gross, 1956; Wolff *et al.*, 1956a, 1956b, 1957a, 1957b). Decreased activity results from expansion of total body water by such procedures as pitressin administration (Beck *et al.*, 1955; Bartter *et al.*, 1956; Muller *et al.*, 1956b).

Increased urinary aldosterone excretion associated with sodium retention has been reported in normal subjects taking a low-sodium diet (Wolff *et al.*, 1957b). Thorn *et al.* (1957), however, found this response variable, and concluded that factors other than increased aldosterone secretion must participate in the response of the kidneys to reduced dietary sodium.

3. Posterior Pituitary Activity

There is considerable evidence to suggest that pituitary antidiuretic hormone (A.D.H.) is involved in oedema formation. Secreted in proportion to osmotic demands (Hare *et al.*, 1941; Corey and Britton 1941), it increases renal tubular reabsorption of water. The osmotic demands are determined by hypothalamic osmoreceptors which excite nervous impulses to stimulate or inhibit A.D.H. secretion whenever the extracellular fluid osmolarity varies above or below a critical level. Cerebral cortical stimulation—for example, emotion—may also influence its secretion.

Increased antidiuretic activity has been found in the urine of oedematous patients with chronic congestive heart failure (Bercu *et al.*, 1950).

In patients with advanced heart failure Miller (1951) has shown that clinical improvement following treatment is associated with a relatively greater loss of water than of sodium. Weston *et al.* (1952) have also reported that when established failure becomes further intensified by superimposed infection, escape from digitalis control, or digitalis toxicity, in patients on free fluid and low-salt intakes, hyponatraemia occurs owing to primary water retention.

Material

The present series comprises 14 patients with chronic congestive heart failure, 13 of whom were treated with prednisolone. An enhanced diuresis was obtained and heart failure was relieved in all 13 patients.

Clinical Evidence of Adrenocortical Deficiency in Chronic Heart Failure

The decision to administer prednisolone to these patients with chronic heart failure was made following clinical observation of two patients in chronic congestive failure. In both patients the preceding history, the clinical signs, and the biochemical investigations suggested an evolving pattern of initial endocrine stimulation succeeded by adrenocortical insufficiency.

Case 1

A 49-year-old man was admitted to hospital with congestive heart failure and auricular fibrillation due to ischaemic heart disease. In the past seven years three attacks of coronary thrombosis had occurred and on five occasions congestive failure had supervened. Influenza four months earlier had precipitated congestive heart failure. Restriction of fluids and salt, diuretic therapy, and increased digitalis dosage produced no improvement. For a month prior to admission, despite these measures and a continued dosage of digitalis folia, 8 gr. (0.54 g.) daily, congestive failure progressed and he developed nightly attacks of left ventricular failure.

Dyspnoeic at rest, his eyes were bright; there was lid retraction and slight diffuse thyroid enlargement. Auricular fibrillation was present with an apex rate of 120 a minute.

His blood pressure was 110/80. The heart was enlarged and he had considerable congestive failure.

After two weeks' treatment with digitalis folia, 8 gr. (0.52 g.) daily, a low-salt diet, bi-weekly mersalyl injections, and chlorothiazide his nocturnal dyspnoea had subsided, but the auricular fibrillation and congestive failure were unaltered and he no longer responded to mersalyl. Excessively drowsy by day, he was restless and disorientated at night. An empirical trial of Lugol's iodine slowed his rate of auricular fibrillation and produced improvement. Thiouracil was substituted for the iodine, but the fibrillation rate steadily accelerated again. A pulmonary embolus finally hastened death six weeks after admission.

Electrolyte and blood urea estimations were made at intervals throughout his final illness (Table I). Despite considerable oedema he developed sodium depletion. Only slight improvement occurred when diuretics were stopped and a normal diet was given. Further slight benefit followed oral salt administration. A marked but transient clinical and biochemical improvement occurred, with an immediate diuresis following subcutaneous infusions of normal saline and M/6 lactate.

TABLE I.—*Case* 1. *Serum Electrolyte (mEq/l.) and Blood Urea (mg./100 ml.) Determinations During Treatment for Chronic Congestive Heart Failure*

Date	Blood Urea	Serum Na	Serum K	Plasma Chlorides	Plasma Alkali Reserve
12/1/57	71	137	5·3	98	25·9
20/1/57	99	—	—	—	—
*22/1/57	57	127	5·3	88	23·7
28/1/57	—	131	6·2	89	22·8
31/1/57	107	—	—	—	—
†1/2/58	—	134	5·6	83	—
‡3/2/58	141	142	6·4	96	17·9
5/2/58	109	151	5·6	97	25·9
7/2/58	129	128	5·8	91	24·2
10/2/58	154	123	6·2	84	20·1
11/2/58	120	—	—	—	—
14/2/58	128	134	6·7	—	20·1
17/2/58	161	124	6·1	90	18·8

* Oral salt therapy.
† Normal saline 3 litres subcutaneously.
‡ M/6 lactate 540 ml. subcutaneously.

Comment.—It was thought that persistent heart failure had induced prolonged hypothalamic - pituitary-peripheral endocrine stimulation. This mechanism, by increasing thyrotrophic hormone activity, could have accounted for the recent onset of hyperthyroidism, previous observation of this patient over a period of seven years having shown no evidence of thyroid excess. Prolonged stimulation of this mechanism to the point of exhaustion, with resulting adrenocortical insufficiency, would explain his salt deficiency, failure to maintain improvement, and inability to retain administered sodium. In these respects and in his excessive drowsiness he resembled a patient with Addison's disease; furthermore, his blood urea and electrolyte levels were in keeping with adrenocortical deficiency.

Case 2

A 76-year-old man was admitted to hospital in congestive heart failure two days after a myocardial infarction. A similar episode had occurred a year previously, since when he had been dyspnoeic on exertion. A diabetic for 37 years, he had been stabilized on 72 units of insulin zinc suspension daily for the last four years.

He was treated with digoxin, twice-weekly mersalyl injections, anticoagulants, a 100-g. carbohydrate diet with no added salt, and soluble insulin four-hourly, the dosage being varied according to urine tests.

He slowly improved, but deteriorated again 10 days after admission. His congestive failure increased, distressing Cheyne-Stokes respiration occurred, and he developed attacks of left ventricular failure which became progessively more frequent. By the fourteenth day he was moribund and had pulmonary oedema. At this stage it was noticed that his insulin requirements had fallen over the previous four days from 80 units daily to zero, and this was corroborated by blood-sugar determinations. Intramuscular hydrocortisone was administered; frequent injections of morphine were required to relieve attacks of acute dyspnoea.

He remained semicomatose for 24 hours and intramuscular hydrocortisone was continued. After 36 hours a remarkable improvement occurred. He was bright and alert, his dyspnoea had vanished, and an increasing diuresis ensued; after 72 hours jugular venous congestion had subsided and only a trace of sacral oedema remained. Hydrocortisone was replaced by oral prednisolone. This improvement was sustained for six days and was terminated by collapse following a pulmonary embolus. Congestive failure recurred, and, despite increased prednisolone dosage, his condition deteriorated, his blood pressure varying between 80/55 and 90/75. A noradrenaline infusion (4 mg./litre) was started, but within 10 minutes of starting this therapy, with a drip rate of 50 a minute, he developed ventricular fibrillation and died.

Comment. — Diabetic patients commonly show increased insulin tolerance when subjected to stress, a phenomenon that has been attributed to adrenocortical stimulation. Decreased insulin requirements occur, with recovery after removal of stress. That the initial aggravation of this patient's diabetes might be associated with increased adrenocortical activity is supported by the finding of increased urinary aldosterone excretion in patients following myocardial infarction (Wolff *et al.*, 1957b). Later, however, decreasing insulin requirements and blood-sugar levels were associated paradoxically with a worsening clinical state. There is much experimental evidence to suggest that severe diabetes is associated with anterior pituitary overactivity, with resulting adreno-glucocorticoid excess. It was thought that long-standing diabetes in this patient had been associated with prolonged overstimulation of the pituitary-adrenal axis. His myocardial infarction, by creating further demands for adrenocorticoids, had exhausted this mechanism. The improvement which occurred in this patient, who had been *in extremis* when prednisolone was administered, conflicted with the accepted view that steroid therapy is contraindicated in patients with congestive heart failure. From the hypothesis that chronic heart failure is associated with adrenocorticoid insufficiency it follows that steroid therapy is *indicated* in such cases to correct this deficiency.

These principles were applied to the treatment of a patient with chronic heart failure and hyponatraemia whose failure had become resistant to traditional therapy. A profuse diuresis with relief of heart failure followed the administration of prednisolone.

Case 3

A 68-year-old woman was admitted with congestive heart failure of two years' duration due to ischaemic heart disease. Over this period dyspnoea had steadily increased in spite of digitalis therapy, and three weeks before admission her failure worsened after an attack of bronchitis. She had been a chronic winter bronchitic for 10 years. Her blood pressure was 130/80.

After two weeks' treatment her congestive failure had progressed. She became noisy and disorientated at night, with drowsiness by day, and was found to have a sodium deficiency (Table II). A normal diet was given and chlorothiazide therapy stopped, but mersalyl was continued twice weekly. Decreased drowsiness coincided with a rise in serum sodium from 121 to 133 mEq/l., but her oedema

TABLE II.—*Case 3. Serum Electrolyte (mEq./l.) and Blood Urea (mg./100 ml.) Estimations*

Date	Blood Urea	Serum Na	Serum K	Plasma Chlorides	Plasma Alkali Reserve
During standard therapy					
25/2/58	42	—	—	—	—
9/3/58	60	121	—	90	25·0
26/3/58	77	133	4·4	97	23·7
10/4/58	120	139	5·7	91	18·8
24/4/58	53	134	5·0	93	22·8
During additional prednisolone administration					
28/4/58	41	137	4·8	104	26·3
5/5/58	51	141	5·0	98	28·6
23/5/58	32	143	4·3	96	29·5
*11/8/58	30	139	5·1	96	31·3

* After three months' out-patient treatment.

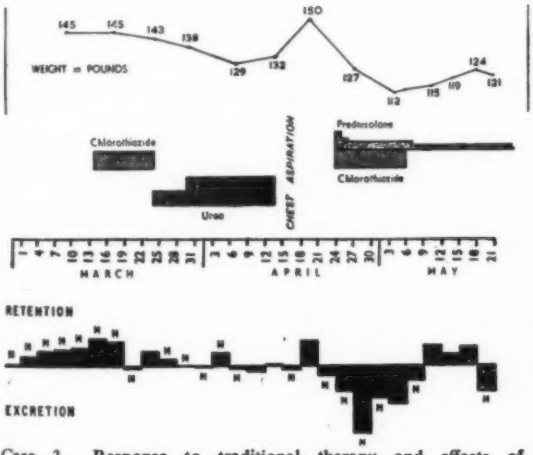
increased and the blood urea rose to 77 mg./100 ml. In order to avoid further salt depletion urea was administered as a diuretic, but the resulting slight decrease in oedema was attended by an increase of blood urea to 120 mg./100 ml. and retention of fixed base (Na, 139 mEq; K, 5.7 mEq./l). A fall in blood urea to 53 mg./100 ml. following cessation of urea therapy was associated with a decrease in serum sodium to 134 mEq/l. Mersalyl therapy was then stopped in order to prevent further urinary loss of sodium, but oedema steadily accumulated and she developed a pleural effusion which required aspiration.

After two months' treatment an overall gain of 5 lb. (2.27 kg.) in weight reflected the increase in oedema and ineffectiveness of therapy. At this stage her plasma proteins were 7.5 g./100 ml. and, despite hyponatraemia, oedema was increasing.

Oral prednisolone was started in a dosage of 5 mg. q.d.s. for the first 24 hours, 2.5 mg. q.d.s. for the next 24 hours, and 2.5 mg. t.d.s. for 12 days, after which a maintenance dosage of 2.5 mg. b.d. was continued together with digitalis and twice-weekly mersalyl.

A diuresis occurred within 24 hours of starting prednisolone, and a greatly enhanced response to mersalyl was apparent. Within 10 days all congestive phenomena had disappeared, and over a period of two weeks a weight loss of 38 lb. (17.2 kg.) was recorded (see Chart). On discharge there was no evidence of congestive heart failure and her serum electrolytes and blood urea had returned to normal levels.

She has been maintained on digitalis, twice-weekly chlorothiazide, and potassium chloride in standard dosage with prednisolone 2.5 mg. b.d. Followed as an out-patient for six months, she has continued to improve, and has lost a further 6 lb. (2.7 kg.) in weight. Within a month of leaving



Case 3. Response to traditional therapy and effects of prednisolone administration on fluid balance and body weight. M=Mersalyl administration.

hospital she was able to walk more than one mile (1.6 km.) to keep her hospital appointment, and so well does she feel that she can do all her own housework and shopping and is free from dyspnoea.

Comment.—It is perhaps significant that this patient had bilateral exophthalmos; there was, however, no evidence of hyperthyroidism. She was also hirsute and pigmented. These physical signs could be interpreted as evidence of past thyrotrophic hormone and adrenocortical excess provoked by prolonged heart failure and succeeded by ultimate anterior pituitary–adrenocortical exhaustion.

Adrenocorticoid Excretion in Chronic Heart Failure

More substantial evidence of adrenocortical insufficiency in chronic heart failure was obtained by measuring the urinary excretion of 17-ketosteroids in four patients with chronic congestive failure. In two of these patients the urinary corticoid excretion was also measured. The 24-hour urinary steroid excretion was considerably reduced in all four patients, one having values compatible with Addison's disease (Case 4). Furthermore, the ability of corticotrophin to increase the urinary excretion of these adrenocorticoids indicated that the deficiency existed at pituitary rather than adrenal level (Table III).

TABLE III.—*Urinary Adrenocorticoid Excretion (mg./day) in Chronic Heart Failure, Before and After Corticotrophin Administration*

Case No.	Before Corticotrophin		After Corticotrophin	
	17-Ketosteroids	Corticoids	17-Ketosteroids	Corticoids
4	<1	2·8	<1	6
4*	—	—	2·2	10·8
5	2·8	—	3·0	—
6	1·2	4·8	2·9	16·6
10	2·7	—	3·7	—

* After corticotrophin 60 units b.d. for one month.

Case 4

A 49-year-old woman with rheumatic mitral stenosis and incompetence, tricuspid incompetence, auricular fibrillation, and cardiac cirrhosis with ascites was admitted to hospital in congestive heart failure.

Heart failure had first intervened 16 years previously and had not subsided despite treatment and close supervision in the last eight years, during which time periodic exacerbations had necessitated frequent admissions to hospital. Following mitral valvotomy six years earlier, she had improved for one year, but further severe exacerbations of congestive failure, each becoming progressively more resistant to treatment, forced a second valvotomy four years later. By that time cardiac cirrhosis had developed and only slight symptomatic benefit was obtained. In the last two years persistent ascites and a right pleural effusion had required repeated aspiration.

Apart from the signs in her cardiovascular system she was frail and pigmented, the pigmentation being particularly marked on the extensor surfaces of the limbs, on the neck, and in the palmar creases. The skin was dry and atrophic, her hair was of fine texture and dry, pubic hair was scanty, and axillary hair absent. A small nodule was palpable in the thyroid.

Her urinary 17-ketosteroid excretion was less than 1 mg. in 24 hours and was unaltered after administration of intramuscular corticotrophin 40 units q.d.s. for four days. Following intramuscular corticotrophin 60 units b.d. for one month the urinary excretion of 17-ketosteroids increased to 2.2 mg. a day. Corresponding values for the excretion of corticoids were 2.8 mg. initially and, following corticotrophin administration, 6 mg. after four days and 10.8 mg. after one month (Table III).

With corticotrophin therapy and a fixed dietary sodium and potassium intake of 250 and 35 mEq. daily respectively her initial sodium deficiency was corrected and during this period the increasing urinary loss of sodium (Table IV) reflected the increased serum sodium level (Table V). The

TABLE IV.—*Case 4. Urinary Excretion of Sodium and Potassium During Corticotrophin Therapy*

Date	Na	K
5/6/58	30 mEq/day	108 mEq/day
6/6/58	39 ,,	49 ,,
12/6/58	57 ,,	28 ,,
17/6/58	78 ,,	62 ,,

Na intake 250 mEq/day. K intake 35 mEq/day.

TABLE V.—*Case 4. Serum Electrolyte (mEq/l.) and Blood Urea (mg./100 ml.) Values Before and During Corticotrophin Administration*

	Serum Na	Serum K	Serum Chlorides	Plasma Alkali Reserve	Blood Urea
Before corticotrophin ..	136	4·4	95·7	30·8	36
During ,, ..	142	3·4	94·0	33	34

fall in both urinary potassium excretion and serum potassium level was presumed to be due to a movement of extracellular potassium into the cells. During corticotrophin administration her blood pressure increased from 100/60 to 115/80 and coincided with an increase of serum sodium from 136 to 142 mEq/l. The serum potassium decreased over this period from 4.4 to 3.4 mEq/l.

Effects of Prednisolone Administration in Patients with Obstinate Heart Failure

Prednisolone was administered to 13 patients with chronic congestive heart failure which had become resistant to traditional therapy. Hyponatraemia was present in each instance and with one exception (Case 4) the blood urea was raised, usually from 50 to 100 mg./100 ml. All patients showed excessive tiredness; the majority had increased skin pigmentation, some having well-marked buccal pigmentation which could easily have been missed had it not been sought specifically. Of the nine women, six had thyroid adenomata.

Existing therapy with digitalis and diuretics was supplemented with prednisolone in a dosage of 5 mg. t.d.s. for the first 24 to 48 hours followed by a maintenance dosage of 2.5 mg. twice or thrice daily. A normal diet was substituted for the low-salt regimen.

A rapid and sometimes dramatic improvement occurred within three or four days of starting prednisolone therapy. Symptoms were relieved and a diuresis was established, with disappearance of oedema and congestive failure within two to four weeks (Table VI). A slower response was obtained in one patient, a woman of 67 with chronic nephritis in addition to her chronic congestive heart failure.

After the patient's discharge from hospital prednisolone maintenance therapy and digitalis were continued. In addition each patient received oral chlorothiazide 0.5 g. b.d. and potassium chloride 1 g. b.d. on two or three days each week.

Although a diuresis occurred in some patients when digitalis therapy alone was supplemented with prednisolone, it was slight when compared with the greatly enhanced response obtained with the additional administration of diuretics. Temporary withdrawal of diuretic therapy resulted in a considerably reduced urinary output, and in some patients fluid retention with a gain in weight occurred (see Chart).

The diuresis-promoting effect of delta-hydrocortisone has been reported previously. Thus Bickerman *et al.* (1955) showed that a weight loss in 20% of their patients with bronchial asthma and pulmonary fibrosis during prednisone therapy was due to an increased urinary output. A marked diuresis was reported by Cattan and Vesin (1956) when four patients with anasarca were treated with prednisone. There have been reports of considerable improvement in patients with obstinate heart failure whose unresponsiveness to the usual therapy, particularly diuretics, has been reversed during prednisone administration. Bickel (1955) has described two such cases, Riemer (1956) one case, Muller *et al.* (1956a) two cases, and Gutner *et al.* (1957) five cases. These reports have not revealed uniform success, some patients with heart failure having failed to respond to steroid therapy. Thus Gutner *et al.* (1957) treated 11 patients in *varying stages* of heart failure with prednisone; only five benefited with decreased shortness of breath, and only three of these lost weight; the sixth patient had increased dyspnoea and gained weight, whilst the remaining five patients showed no change in their cardiac status.

Endocrine Adjustments in Chronic Heart Failure

Patients in this series exhibited phenomena suggesting adrenocortical deficiency. This evidence was based upon the following criteria: (*a*) The clinical observation of excessive tiredness and increased skin pigmentation with associated buccal pigmentation in some patients. (*b*) All patients had developed a sodium deficiency in association with a normal or elevated serum potassium

TABLE VI.—*Patients with Obstinate Congestive Heart Failure which Responded to Prednisolone Therapy*

Case No.	Age and Sex	Aetiology	Duration of Failure	Weight Loss lb.	Weight Loss kg.	Weight Loss Weeks	Follow-up
2*	76 M	C.I.	Intermittent, 1 year	—	—	—	Died after 1 week. Pulmonary embolus
3	68 F	C.I. Chronic bronchitis	,, 2 years	38	17·2	2	6 months
4	49 F	Rheumatic heart disease. A.F.	16 years	7	3·2	2	5 ,,
5	67 F	Hypertension, bronchial asthma, chronic bronchitis, gastro-intestinal haemorrhage	3 months	21	9·5	5	2 ,,
6	60 M	Rheumatic and ischaemic heart disease. A.F.	Intermittent, 8 years	4	1·8	1	1 month
7	77 F	Calcareous aortic stenosis and incompetence	3 weeks	8	3·6	4	3 months
8	67 F	Rheumatic heart disease. A.F.	Intermittent, 4 years	4½	2·0	3	5 ,,
9	60 F	,,	8 months	3	1·4	2	5 ,,
10	63 F	C.I. Hypertension. Chronic nephritis	Intermittent, 7 years. Continuous, 2 years	9	4·1	3	2 ,,
11	82 F	C.I.	Intermittent, 10 years	18	8·2	4	1 month
12	69 M	,,	,, 8 ,,	14	6·4	4	3 months
13*	80 M	,,	,, 8 ,,	—	—	—	Died after 2 weeks. Pulmonary embolus
14	41 F	Rheumatic heart disease. A.F.	,, 10 ,,	12	5·4	3	3 months

* Heart failure subsided before death. C.I. = Cardiac ischaemia. A.F. = Auricular fibrillation.

level and raised blood urea. (*c*) Estimation of urinary 17-ketosteroid excretion in four patients and of corticoid excretion also in two of these patients revealed considerably reduced values. The increased urinary excretion of these steroids following adrenal stimulation with corticotrophin indicated that failure had occurred at anterior pituitary rather than adrenal level.

The possibility of adrenocorticoid insufficiency is supported by the disappearance of heart failure following correction of this deficiency with prednisolone.

These results, considered in conjunction with those previously recorded in patients with congestive heart failure, suggest a pattern of events contributing to the formation of oedema.

The initial phase of heart failure is associated with a primary salt retention resulting from enhanced tubular reabsorption of sodium. This is achieved by a decrease in glomerular filtration rate aided by baseline aldosterone activity independent of pituitary control. In some instances the ensuing secondary water retention, determined by simple osmotic equilibrating forces, by expanding the extracellular fluid, is sufficient to restore the effective circulating blood volume, and thereby repairs the discrepancy between cardiac output and tissue metabolic requirements.

Should these mechanisms prove inadequate they are reinforced by anterior and posterior pituitary stimulation mediated via the hypothalamus. Increased corticotrophin secretion encourages further aldosterone production in addition to other corticoids. A primary water retention follows increased posterior pituitary antidiuretic activity. As a result of anterior pituitary stimulation thyrotrophic hormone secretion is also augmented. Clinically this was evidenced by auricular fibrillation controlled with Lugol's iodine in Case 1 and by the presence of exophthalmos in Case 6. In both patients long-standing heart failure could have resulted in prolonged thyrotrophic hormone excess. This mechanism could also account for the finding of thyroid adenomata in six of the nine women in this series. Enhanced thyroid activity by increasing metabolism in patients with *recent* congestive failure could account, in part, for the well-recognized elevation in metabolic rate associated with heart failure. In these patients the increase in circulating thyroid hormone would serve a double purpose. By potentiating the action of adrenaline it would assure continued efficient anterior pituitary stimulation, and by increasing adrenocortical metabolism would encourage further corticoid production.

These mechanisms are probably all invoked in varying degree in congestive heart failure and can be reversed by treatment which restores the cardiac output to a level sufficient for tissue metabolic needs. Traditional therapy achieves this object, with digitalis administration improving the cardiac output while rest in bed induces a synchronous reduction in tissue metabolism. With correction of this discrepancy the endocrine and renal haemodynamic adjustments revert to normal. The previously expanded extracellular fluid is, however, slow to subside, a fact clinically apparent in the persistence of oedema for varying periods after jugular venous congestion has disappeared. The tardy excretion of extracellular fluid, by delaying contraction of the circulating blood volume, embarrasses the cardiac pump. Diuretics speed recovery by hastening the elimination of this unnecessary salt and water.

Adrenal cortical deficiency occurring in patients with *chronic* congestive heart failure in this series resulted from anterior pituitary failure. This suggests that the continuing necessity for these endocrine-adjusting mechanisms leads to exhaustion of anterior pituitary function. Persisting posterior pituitary overstimulation would then induce excessive antidiuretic hormone activity and a primary retention of water in association with adrenocortical insufficiency.

At this late stage of heart failure excessive secretion of antidiuretic hormone remains as the predominant mechanism reinforcing aldosterone activity, thereby sustaining the defective circulation.

It is unlikely that digitalis therapy and bed rest alone will relieve heart failure at this stage. The response to diuretic therapy will be poor in the presence of hyponatraemia ; indeed, by inducing only slight urinary loss of sodium with secondary water loss diuretics will stimulate further water retention and merely encourage the state of obstinate heart failure. By correcting the adrenal deficiency with hydrocortisone in physiological quantities and continuing as maintenance therapy, hyponatraemia will be relieved and so-called "irreversible" heart failure will revert to the earlier phase and become responsive to traditional therapy.

This hypothesis offers an explanation for the salt-deficiency syndrome which occurs in patients with congestive failure when intercurrent infection supervenes and during periods of hot weather. In either circumstance adrenocortical demands, secreted in response to corticotrophin stimulation, are increased. The pituitary-adrenal mechanism, already fully extended in response to congestive failure, becomes exhausted, antidiuretic hormone overactivity persists, and water retention occurs, with resulting tissue fluid hypotonicity. Injudicious salt deprivation or diuretic therapy, by further increasing the demands for aldosterone, will for similar reasons favour the development of the salt-deficiency syndrome. Under the circumstances described this syndrome would occur more readily in elderly patients whose pituitary-adrenal reserves are reduced.

Mode of Action of Prednisolone Therapy

The urinary sodium excretion was not determined in the patients in this series. It is, however, unlikely that their prednisolone-induced diuresis was due to increased urinary loss of sodium, since they all had a decreased serum-sodium level prior to steroid therapy, and this increased and remained at a normal level despite a profuse diuresis. It must be assumed that the increased urinary output was due to a *predominant* water diuresis.

Anterior pituitary exhaustion could account for the beneficial effects obtained with prednisolone therapy.

1. Correction of adrenocortical deficiency would relieve intracellular overhydration by virtue of the known action of steroids in causing a movement of intracellular water and sodium into the extracellular compartment ; furthermore, they would promote a simultaneous transfer of potassium in the opposite direction. These electrolyte readjustments would partly account for the rise in serum-sodium level and would also explain the decreased serum-potassium level despite decreased urinary potassium excretion in Case 4 (Table IV). This action would not, however, result in a water diuresis.

2. It has been established that an antagonism exists between adrenocortical and posterior pituitary antidiuretic hormones

at the level of the renal tubule (Talbot *et al.*, 1952). This antagonism would explain the increased urinary output in these chronic cardiac patients, a water diuresis occurring when the renal tubules are released from excessive unantagonized antidiuretic activity by the intervention of prednisolone. Furthermore, this mechanism would support the hypothesis that obstinate oedema in these patients was due to excessive posterior pituitary activity in the presence of adrenocortical insufficiency.

3. Other known effects of steroid therapy, although contributory, probably played only a minor part in the diuresis. Thus, in normal subjects steroids increase the glomerular filtration rate; by favouring corticogenic hypothyroidism they could decrease the work load upon the heart and by increased mobilization of glucose they would improve myocardial function. They might confer additional benefit by increasing pulmonary ventilatory capacity, and by virtue of their erythropoietic action would correct anaemia if present.

4. Muller *et al.* (1956a) and Gutner *et al.* (1957) have reported beneficial results following prednisone administration to patients with heart failure resistant to the usual therapy. These authors attributed improvement, in those patients who showed a diuresis, to suppression of anterior pituitary function by prednisone therapy with a consequent reduction of endogenous aldosterone secretion. This explanation is supported by the diminished excretion of urinary "sodium-retaining factor" following cortisone administration (Luetscher and Deming, 1950; Luetscher *et al.*, 1951) and also by the decrease in urinary aldosterone excretion in patients receiving prednisone (Mach and Muller, 1956). In addition Muller *et al.* (1956a) showed that the combination of prednisone with acetazolamide or mercaptomerin lowered the urinary aldosterone excretion to a greater extent than did prednisone administration alone. These same diuretics usually produced an increase of aldosterone when administered alone.

A decrease in extracellular fluid volume following diuresis would be expected to stimulate aldosterone activity. Although it is possible that prednisolone by suppressing anterior pituitary function prevented this overactivity, if this be the only mechanism by which diuresis and improvement occur, all patients to whom Muller and Gutner and their colleagues administered prednisone should have gained benefit. Their results, however, were not uniformly successful. In the present series the evidence suggested that anterior pituitary function was already greatly depressed, and it is doubtful whether the physiological quantities of prednisolone they received would have caused further anterior pituitary suppression.

The failure to obtain uniformly successful results could lie in the fact that the patients to whom Gutner and his co-workers administered prednisone were in "varying stages of heart failure." Only those patients who had reached the stage of anterior pituitary exhaustion would respond to prednisone therapy.

Discussion

Although patients in this series had evidence of hypoandrenocorticism it should be emphasized that this had resulted from anterior pituitary insufficiency. The oedema which they exhibited could not have been due to hypoadrenocorticism alone, since oedema is not part of the clinical picture of Addison's disease. In this latter condition adrenal destruction results in *total* adrenocorticoid deficiency, and, moreover, since there is no stimulus to posterior pituitary overactivity, fluid retention does not occur. Hyponatraemia in these patients with late-stage heart failure, although encouraged by lack of adrenal ketosteroids and hydroxysteroids, was probably due largely to water retention and increased intracellular sodium, since prednisolone administration, a normal diet, and diuretic therapy induced a profuse diuresis with a concomitant rise in serum-sodium levels.

Urinary aldosterone excretion was not estimated, but baseline aldosterone secretion, being independent of pituitary function, was probably unaffected in these patients. It may even have been increased, as the patients with chronic heart failure reported by Muller *et al.* (1956a) all had excessive urinary aldosterone excretion. Such excess, however, could not alone account for the oedema in these patients, since they had a predominant water retention; furthermore, oedema does not occur in primary hyperaldosteronism (Conn, 1955). The latter condition differs in its pathogenesis from the hyperaldosteronism of heart failure and is unassociated with posterior pituitary stimulation; indeed, the contrary might be expected, and could explain the absence of oedema in primary hyperaldosteronism.

The increased urinary aldosterone excretion found in patients with the nephrotic syndrome and the diuresis they experience following corticotrophin or cortisone administration suggest that oedema in this condition has a similar pathogenesis to that of late-stage heart failure. Such patients would differ only with respect to the primary cause of pituitary stimulation, which, in nephrosis, would occur in response to excessive urinary electrolyte loss resulting from renal damage.

A parallel with famine oedema is also suggested, since analogous electrolyte changes and evidence of adrenocortical deficiency occur in patients under starvation conditions (Hubble, 1952). These findings reflect extended adjustments by the pituitary-endocrine mechanism in order to adapt the functioning organism to the extreme nutritional poverty and eventual anterior pituitary exhaustion with residual posterior pituitary excess.

The observation of Hollander and Judson (1956) that salt retention does not occur in patients with isolated left ventricular failure has been clarified by Wolff *et al.* (1957b), who found no increase in urinary aldosterone excretion in patients with isolated left ventricular failure, in contrast to the excessive aldosterone excretion associated with congestive heart failure. That adrenocorticoid *deficiency* may contribute to cardiac asthma and pulmonary oedema is suggested by the prompt relief and disappearance of attacks of left ventricular failure which occurred in five patients in this series following prednisolone therapy. In this respect Prasad (1958) has reported that prophylactic prednisone administration protected experimental animals from pulmonary oedema.

In congestive heart failure the striving to maintain parity between the cardiac output and the tissue's metabolic needs results in progressive adaptations by the pituitary-peripheral endocrine system, particularly with regard to adrenal function. The inherent qualities of this system become apparent in the paradox which evolves as the adjustments fail to achieve their aim. Eventually the patient with chronic heart failure, by virtue of anterior pituitary exhaustion, regulates metabolism in response to cardiac output and, with this precarious but only available existence, exhibits a complete reversal of the normal status.

In view of the steroid structure of digitalis the hypothesis advanced in this paper may offer an explanation for the mode of action of this drug in patients with heart failure.

Summary

Factors which contribute to salt and water retention in congestive heart failure are reviewed, with particular reference to the endocrine system.

Clinical observation of 14 patients with chronic congestive heart failure suggested an initial coexistent endocrine overactivity followed subsequently by adrenocortical insufficiency.

This premise was supported by the presence of hyponatraemia, a normal or elevated serum-potassium level with an increased blood urea in 14 patients with chronic heart failure which had become resistant to therapy with digitalis, a low-salt diet, and diuretics.

The urinary excretion of 17-ketosteroids was estimated in four of these patients, and in two the corticoid excretion was also assessed. Subnormal values were obtained in each instance, and in one patient were consistent with a diagnosis of Addison's disease. Following corticotrophin administration the urinary excretion of these steroids increased in each patient and was accepted as evidence that hypoadrenocorticism was due to anterior pituitary rather than adrenocortical failure.

Replacement therapy, using prednisolone, induced a greatly enhanced response to diuretics in all 13 patients who received this treatment. All were relieved of congestive heart failure and also, when coexistent, of left ventricular failure. Two patients died following pulmonary emboli.

A hypothesis is advanced regarding the endocrine adjustments which occur in heart failure and which could lead to the formation of oedema. The importance of these adjustments is described in relation to the treatment of heart failure.

The possible mode of action of prednisolone is discussed.

Parallels are drawn between the oedema of late-stage congestive heart failure, nephrotic oedema, and starvation oedema.

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CHLORMERODRIN: CLINICAL EFFECTIVENESS AND ABSENCE OF TOXICITY IN CONGESTIVE HEART FAILURE

REPORT OF A FOUR-YEAR STUDY

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Organomercurial diuretics are widely recognized as the most potent and reliable of available diuretic agents. Until recently, satisfactory organomercurial preparations were available only for administration by injection, limiting their acceptability to patients. From the clinical standpoint, a need also existed for an oral organomercurial which could be administered frequently in relatively small doses. Such an agent would provide continuous diuresis, rather than the seesaw of dehydration and rehydration that occurs with the less frequent higher doses ordinarily employed when a diuretic is given by injection. Chlormerodrin ("neohydrin"*: 3-chloromercuri-2-methoxypropylurea), a non-ionic crystalline compound introduced in 1952, showed early promise of meeting this need. Our

*Neohydrin supplied through the courtesy of Dr. H. L. Daiell, Lakeside Laboratories, Inc., Milwaukee, Wis.

own preliminary clinical study (Leff and Nussbaum, 1953) indicated that most patients who had previously required meralluride (" mercuhydrin ") injections at least once a week did as well or better on three or four tablets of chlormerodrin daily. Side-effects were few and not of a serious nature. Similar findings have been presented by other investigators (Moyer *et al.*, 1952; Finch, 1952; Mauriello and Re, 1953; Kaplan *et al.*, 1953; Bresnick and Abramson, 1953; Lawrence *et al.*, 1954; Doherty *et al.*, 1954; Küchmeister and Kristal, 1955; Ginefra, 1955; Hvidsten, 1955; Moyer and Hughes, 1955; Evans and Massumi, 1956).

The observations over a four-year period now presented were made with particular attention to the relative safety of chlormerodrin. Whenever organomercurials are used as therapeutic agents, fear of their possible toxicity is likely to be expressed. Although we consider this fear to be unwarranted when modern organomercurial preparations are used, we remained aware that the following questions regarding the safety of these agents have not been fully answered: What are the possibilities that *inorganic* mercury will be deposited in the tissues during the course of therapy with *organic* mercurials? How much mercury can be quantitatively demonstrated in the kidney and other vital organs after extensive use of mercurial diuretics? Does impairment of renal function or permanent renal damage result from their use?

Over the period of study our patients were taking very large amounts of chlormerodrin by mouth following many years of treatment with parenteral meralluride. In pursuing our investigation we therefore laid great emphasis on obtaining kidney-function tests on the patients. Clinically, attention was focused for any evidence of renal insufficiency or renal damage. The overall plan also included histological study of tissues obtained at necropsy for evidence of mercurial damage, and quantitative tissue analysis for " metallic mercury " in the whole organs.

Clinical Results

During a four-year period 48 patients in chronic congestive heart failure have been maintained in fluid balance with the use of chlormerodrin, maintenance digitalis, and low-salt diet. Five additional patients developed gastro-intestinal symptoms—nausea, loss of appetite, vomiting, and diarrhoea—and could not tolerate the drug, regardless of rest periods or reduced dosage. These five cases were regarded as failures, and are not included in this long-term report.

The initial functional classification of the patients varied from class II to class IV, under the criteria of the New York Heart Association. Those in class IV were reduced to class II or III by active treatment with parenteral meralluride before changing to the oral regimen with chlormerodrin. It should be noted that continuance of the improved cardiac function was dependent on continued diuretic therapy. Most of the patients had received parenteral diuretic for several years before the change to chlormerodrin was made.

The aetiology of heart disease was varied (Table I). The ages ranged from 29 to 80 years (Table II), 65% being in the sixth and seventh decades. Dosage of chlormerodrin varied with response and tolerance of the patients (Table III).

Of the 48 patients, 43 were maintained free from any signs or symptoms of congestive failure, and did not require additional parenteral mercurials. Five did require occasional booster injections of meralluride in addition to the daily chlormerodrin. After several weekly injections of meralluride, these patients were again able to be maintained on the daily oral mercurial for as long as three to seven months before requiring additional meralluride. Three patients developed diarrhoea taking four tablets daily. They were kept off the drug for two weeks, and then resumed, taking one tablet a day for a week and increasing the dose each week until three tablets a day were being taken after meals. One of these three patients developed soft stools about every fourth month during a three-year period. The remaining two developed diarrhoea in a single instance only. Evans and Massumi (1956) have pointed out, in this connexion, that the patient with heart failure and hepatoportal congestion often has gastro-intestinal symptoms, similar to those produced by drug irritation, which may clear up as the liver and intestines are unburdened of oedema. None of the patients developed any symptoms of mercurialism, or any similar reactions ascribable to hypersensitivity to mercurials.

Our experience with chlormerodrin has conclusively proved its effectiveness as a thoroughly safe and potent " continuous diuretic " agent. Once the dry-weight level was achieved with parenteral meralluride, the seesaw of accumulation and dehydration was rarely seen. The steady diuretic effect of chlormerodrin was in sharp contrast to the intermittent diuretic effect of periodic injections. In several patients, however, an occasional booster shot of the parenteral agent seemed to enhance the steady action of the oral organomercurial. The 48 patients included in this report showed no evidence of mercurial toxicity, as manifested by skin reactions, allergic phenomena (hypersensitization to mercury), renal damage, cardiovascular reactions, bone-marrow depression, or systemic reactions.

Effectiveness in the older age groups was striking. It is obvious that men and women in myocardial failure are now living much longer, owing to more accurate diagnosis, newer glycosides, sodium-restricted diets, and the use of effective non-toxic organomercurials. It should be emphasized that the aged can tolerate oral organomercurials effectively and without renal toxicity.

In the four years of our study the combined total of mercury contained in both parenteral and oral organo-

TABLE I.—*Aetiology in 48 Cases*

Arteriosclerotic heart disease (A.S.H.D.)	22
Hypertensive cardiovascular disease (H.C.V.D.)	9
,, arteriosclerotic heart disease (H.A.S.H.D.)	2
Rheumatic heart disease (R.H.D.)	10
Luetic heart disease (L.H.D.)	5

TABLE II.—*Age and Sex*

	29	30–39	40–49	50–59	60–69	70–79	80	Total
Male	0	1	5	12	7	1	0	26
Female	1	2	4	6	6	2	1	22

TABLE III.—*Dosage*

Chlormerodrin	Mercury Equivalent	No. of Patients
2 tablets a day	20 mg.	11
3 ,, ,, ,,	30 ,,	29*
4 ,, ,, ,,	40 ,,	8†

* Includes 2 patients maintained on 1 tablet a day after the first 6 and 9 months, respectively.
† Includes 1 patient who occasionally took 6 tablets a day.

mercurials given to 48 patients ranged from 6,240 to 78,560 mg. The majority of the patients—34 (71%) received a combined dosage ranging from 20,000 to 60,000 mg. of bound mercury.

In none of the 48 patients was there any clinical or laboratory evidence of renal impairment or permanent renal damage due to the massive quantities of parenteral and oral organomercurial given over the entire four-year period. In spite of the tremendous total dosages, it will be noted (Table IV) that there were practically no abnormal urinary findings. Seven patients exhibited occasional (1+ to 4+) albuminuria, but it is not unreasonable to suppose that this was due to renal passive congestion, and not to any effect of the diuretic. Race *et al.* (1956), at the Mayo Clinic, reported that albuminuria existed in 88% of a group of 161 patients with congestive failure who had come to necropsy without clinically obvious causes for albuminuria, and who showed no histological changes which would account for albuminuria. There was a tendency for the albuminuria to parallel the severity of the cardiac failure.

Of greater significance in our own laboratory data were the consistent findings of normal blood urea nitrogen throughout this study. In fact, urea nitrogen improved in some patients—a manifestation of improved cardiovascular-renal dynamics. In addition, there were the noteworthy normal findings of blood creatinine, N.P.N., and urea-clearance tests.

Deaths During Study

Eight deaths occurred among the 48 patients, none of which was related to mercury (Table V). Three patients

TABLE IV

Case No.	Age and Sex	Race	Aetiology	Chlormerodrin			Meralluride			Total Mercury Oral and Parenteral (mg.)	Laboratory Studies				
				Daily Dose (Tablets)	Duration (Mths)	Total Mercury (mg.)	Weekly Dose (ml.)	Duration (Years)	Total Mercury (mg.)		Urine	Urea Nitrogen	Creatinine	N.P.N.	Urea Clearance
												(mg./100 ml.)			
1	59 M	C	H.C.V.D.	2 b.i.d.	21	23,520	2	10	40,000	63,520	Normal	12·3 25·0 14·4	1·3	25·0	95%
2	62 M	C	R.H.D.	1 ,,	15	8,400	2	1	4,000	12,400	,,	8·4	1·0	17·4	101%
3	57 F	C	R.H.D.	1 ,,	19	10,640	4	3	24,000	34,640	,,	9·0	0·8	18	94%
4	53 M	C	H.C.V.D.	1 ,,	20	11,200	2	3	12,000	23,200	,,		0·4	22	
5	67 F	C	H.C.V.D.	1 t.i.d.	19	15,960		None		15,960	,,	10·4		21	100%
6	30 M	C	R.H.D.	1 ,,	36	30,240	2	3 1/3	13,330	43,570	,,	12·0		15·0	
7	80 F	C	A.S.H.D.	1 ,,	24	20,160		None		20,160	,,				
8	59 F	C	H.A.S.H.D.	1 b.i.d.	24	13,440	2	1	4,000	17,440	,,				
9	45 M	C	L.H.D.	1 t.i.d.	36	30,240	2	2	8,000	38,240	Alb.; few casts	14·3 12·9	1·4	32·4	155%
10	62 M	C	H.A.S.H.D.	1 ,,	22	18,480	4	1	8,000	26,480	Normal	13·5	1·3	28·2	193% 177%
11*†	29 F	W	R.H.D.	1 ,, 1 o.d.	6 27	12,600	2	2½	10,000	22,600	,,	11·5	1·0	20	
12	59 M	W	A.S.H.D.	1 t.i.d.	30	25,020	1	1	2,000	27,020	,,	12	1·2	12	
13	45 M	W	R.H.D.	1 q.i.d.	24	26,880	4	3	24,000	50,880	,,	11·3			88·4%
14	40 F	W	R.H.D.	1 b.i.d.	16	8,960	1	3	6,000	14,960	Occ. alb.	10	1·6	22	
15	54 M	W	A.S.H.D.	1 t.i.d.	24	20,160	2	1	4,000	24,160	Normal	15·0			
16*†	50 M	C	R.H.D.	1 ,,	24	20,160	2	½	2,000	22,160	,,	10·6 19·2	1·4	30	
17	46 F	C	H.C.V.D.	1 b.i.d.	18	10,080	2	5	20,000	30,080	Alb. trace	15·0	1·2		
18	48 M	W	A.S.H.D.	1 t.i.d.	24	20,160	2	2	8,000	28,160	Normal	12·4	1·1		
19	62 M	C	L.H.D.	1 ,,	24	20,160		None		20,160	Alb. 4+ prior to oral diuretic therapy				
20*	67 F	W	A.S.H.D.	1 b.i.d.	30	16,800	2	2	8,000	24,800	Normal	16·5	2·0		
21*	48 M	C	L.H.D.	1 t.i.d.	36	30,240	2	4	16,000	46,240	,,	15	1·8	28·1	92%
22	58 M	C	H.C.V.D.	1 ,,	42	35,280	2	7	28,000	63,280	,,	22·0	2·0		
23*	67 M	W	H.A.S.H.D.	1 b.i.d.	4	2,240	2	1	4,000	6,240	,,	14·4	1·8		
24	72 M	C	A.S.H.D.	1 t.i.d.	12	10,080	2	2	8,000	18,080					
25	68 F	C	A.S.H.D.	1 ,,	24	20,160	2	2	8,000	28,160	Alb. 4+	10·9	1·8		
26	47 M	W	A.S.H.D.	1 ,,	42	35,280	1	2	4,000	39,280	Normal	11	1·2	24	
27*†	48 F	W	R.H.D.	1 q.i.d.	18	20,160		None		20,160	Alb. 1+	24 21·9	2·1	42 40	
28	59 M	W	A.S.H.D.	1 t.i.d. 1 o.d.	9	10,920	1	2	4,000	14,920	Normal	14	1·4	24	
29	52 M	W	A.S.H.D.	2 b.i.d.	15	16,800	2	2	8,000	24,800	,,				
30*	71 F	C	A.S.H.D.	1 t.i.d.	7	5,880	2	4	16,000	21,880	Occ. alb.	18·0	2·0		
31	57 M	C	A.S.H.D.	2 b.i.d.	24	26,880	4	1	8,000	34,880	Normal	10·1 12·5		24	
32	57 M	W	A.S.H.D.	1 ,,	34	19,040	2	2	8,000	27,040	,,	15			
33	67 F	C	L.H.D.	2 ,,	17	19,040	2	1	4,000	23,040	,,				
34	73 F	C	A.S.H.D.	1 t.i.d.	48	40,320	2	6	24,000	64,320	,,	19·6 10·5	0·9	29·4	109% 125%
35	60 F	W	R.H.D.	1 ,,	30	25,200		None		25,200	,,				
36	49 F	C	H.C.V.D.	2 b.i.d.	18	20,160		,,		20,160	,,	13·8			
37*	65 M	C	A.S.H.D.	1 t.i.d.	12	10,080	2	2½	10,000	20,080	,,	15·4	1·4		
38	56 M	W	A.S.H.D.	1 ,,	24	20,160	2	3	12,000	32.160	,,	14	1·2	30	84% 92%
39	60 M	C	A.S.H.D.	1 ,,	30	25,200	2	1	4,000	29,200	,,				
40	53 F	C	A.S.H.D.	1 b.i.d.	19	10,640		None		10,640	,,	12·4			
41	63 M	C	A.S.H.D.	1 t.i.d.	42	35,280	2	1	4,000	39,280	,,	9·8			
42	64 F	C	A.S.H.D.	2 b.i.d.	38	42,560	2	9	36,000	78,560	,,	10·8	1·4	33	129% 44%
43	58 F	C	H.C.V.D.	1 t.i.d.	36	30,240		None		30,240	Occ. casts	14·7 22·8	1·2 1·8	34·2	66·6% 51·3%
44	55 F	C	H.C.V.D.	1 ,,	22	18,480		,,		18,480	Normal	24·0 18·0			
45	58 M	W	A.S.H.D.	1 ,,	48	40,320	2	5	20,000	60,320	,,	10·7		22	90% 94%
46	38 F	C	R.H.D.	1 b.i.d.	36	20,160	2	4	16,000	36,160	,,	15		38·7	80·2% 90%
47	55 F	C	A.S.H.D.	1 t.i.d.	42	35,280	2	2½	10,000	45,280	,,				100% disability
48	30 F	C	R.H.D.	1 ,,	38	31,920	2	1	4,000	35,920	,,	11·0 15·0	0·9 1·2	27 38	148% 119%

Note.—Complications occurred in the following cases. Case 13: Post-commissurotomy. Case 17: Grade 3 retinopathy. Case 19: Anaemia, luetic nephrosis, and heart block. Case 25: Kimmelstiel–Wilson disease and diabetes. Case 38: An occasional loose stool.
* Died during study. † Necropsy performed. Chlormerodrin contains 10 mg. of mercury per 18·3-mg. tablet. Meralluride contains 39 mg. of mercury per ml. of solution.

died suddenly of coronary thrombosis. They had been completely free of any signs and symptoms of failure up to the day of death. A fourth patient died of toxaemia and acidosis following amputation of a leg necessitated by saddle embolism. She was not in failure at the time of the embolic accident. Another patient had syphilitic heart disease with aneurysmal dilatation of the aorta, and aortic insufficiency, with marked hypertrophy

TABLE V.—*Deaths During Chlormerodrin Study*

Duration	Case No.	Age	Aetiology	Cause of Death
7 months	30	71	A.S.H.D.	Acute coronary thrombosis
4 ,,	23	67	H.A.S.H.D.	,, ,, ,,
12 ,,	37	65	A.S.H.D.	,, ,, ,,
30 ,,	20	67	A.S.H.D.	Embolism to femoral artery; amputation
36 ,,	21	48	L.H.D.	Aortic aneurysm
18 ,,	27	48	R.H.D.	Pulmonary embolism
24 ,,	16	50	R.H.D.	Congestive failure (subclinical)
33 ,,	11	29	R.H.D.	(1) Endocarditis, acute bacterial, of mitral and tricuspid valves. (2) Subacute and chronic pyelonephritis. (3) Nephrosclerosis, benign

of the left ventricle. He died suddenly, following an episode of severe chest pain. Permission for necropsy was not obtained, but the clinical picture suggested a ruptured aneurysm with haemorrhage. He showed no signs of failure up to the time of death.

Permission for necropsy was obtained in the three other patients who died during the study. Detailed case histories on these patients follow.

Case 27

When first seen in the clinic, this patient, a white woman aged 48 with R.H.D., was classified as having mitral stenosis and insufficiency, and questionable aortic insufficiency with slight hypertrophy of the right and left ventricle, class II. She was maintained in fluid balance with digitalis and a low-salt diet for two years. She then presented evidence of acute rheumatic fever, and her failure increased to class IV. She was hospitalized, improving considerably on symptomatic therapy. She was then followed in the clinic as a class II patient, on chlormerodrin (4 tablets daily ; 40 mg. Hg), in addition to maintenance digitalis and a salt-free diet. She remained in fluid balance for 18 months on this regimen. She was later seen by a private physician, who advised her that she did not require digitalis or chlormerodrin. Twelve weeks later she was admitted to the hospital in a moribund condition, with irreversible failure. She did not respond to any therapy, and died suddenly.

Necropsy showed a rheumatic calcified mitral valve and a partially calcified aortic valve with hypertrophy of both right and left ventricles. There was a large haemorrhagic infarct of the right lower lobe. Sections of the kidney

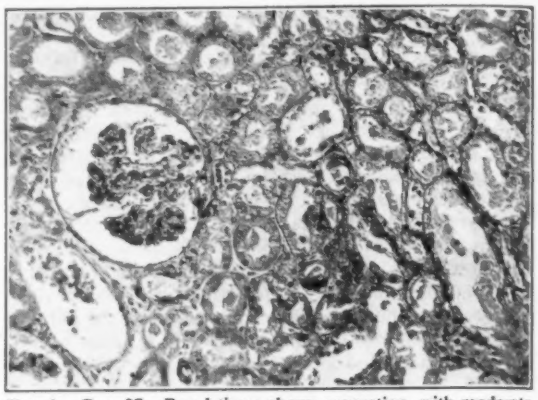


FIG. 1.—Case 27. Renal tissue shows congestion, with moderate glomerulonephritis. (×65.)

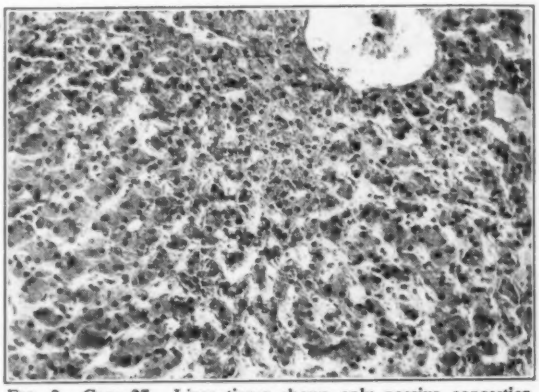


FIG. 2.—Case 27. Liver tissue shows only passive congestion and early mild portal cirrhosis. (×65.)

(Fig. 1) showed cloudy swelling in the tubules with some increased cellularity of the glomerulus. There was no evidence of tubular necrosis. Sections of the liver (Fig. 2) showed congestion around the central vein with haemosiderin deposits. There was no disruption of liver architecture.

The patient received chlormerodrin equivalent to 20,160 mg. Hg. Analysis of the internal organs for retention of mercury demonstrated that the kidney contained only 11.48 mg. Hg per 100 g. of dry tissue. Comparable amounts for the other organs are shown in Table VI.

Case 16

This patient, a coloured man aged 50 with R.H.D., had rheumatic aortic stenosis, mitral stenosis, and insufficiency. He was graded class II and was kept in fluid balance with

TABLE VI.—*Tissue Analysis for Mercury*

	No. with Renal Disease Unrelated to Mercury, Found at Necropsy	Organo-mercurials (Total mg. Hg)	Kidney	Liver	Heart	Spleen	Large Intestine	N.P.N. Studies			
			(mg. Hg per 100 g. Dried Tissue)					Patients	No. Uraemic	Range in Non-uraemics (mg./100 ml.)	Average of All Patients (mg./100 ml.)
Griffith and others (1954)*											
15 cases	9	None	2·05	0·37	—	0·12	—	4 cases	1	55–115	122
14 ,,	9	400 or less	2·96	0·34	—	0·04	—	8 ,,	2	33–88	66
16 ,,	12	400 or more (av. 4,692)	15·29	1·38	—	0·32		6 ,,	1	36–82	73
Present Study											
Case 27	0	20,160	11·48	0·694	0·0144	—	1·34	40 mg. of N.P.N. per 100 ml.			
,, 16	0	22,160	9·63	0·474	0·0006	—	0·40	42 ,, ,, ,, ,, ,, ,,			
,, 11	+	22,600	15·68	0·773	None	0·221	7·3	30 ,, ,, ,, ,, ,, ,,			
								20 ,, ,, ,, ,, ,, ,,			

* Values for mercury shown are averages for patient groups.

chlormerodrin (equivalent to 30 mg. Hg daily) for two years, along with maintenance digitalis and a salt-free diet. He received 2 ml. of meralluride for six months prior to attending the cardiac clinic.

He developed a bradycardia of 40 with A-V block, and had several episodes of Stokes–Adams syndrome. During these attacks he did not show any clinical signs of failure. The last episode of syncope, for which he was hospitalized, showed electrocardiographic evidence of complete dissociation with a ventricular rate of 34. In the ensuing ten days he slowly developed irreversible myocardial failure in spite of all therapy and died on the twelfth hospital day.

Necropsy showed aortic and mitral stenosis with hypertrophy of the right and left ventricles. Sections of the kidney showed no tubular necrosis (Fig. 3). The basement membrane of the tubules appeared sharp, without any disruption of its normal architecture. Sections of the liver showed congestion about the central vein with deposits of haemosiderin (Fig. 4). There was no damage to the liver cells.

This patient received chlormerodrin and meralluride equivalent to 22,160 mg. Hg. Analysis of tissues for mercury, however, showed a concentration of only 9.63 mg. per 100 g. of dry tissue, and correspondingly small amounts in other organs. Note that the amount detected in cardiac tissue was negligible (Table VI).

Case 11

This patient, a white woman aged 29 with R.H.D., was a class II cardiac case with mitral stenosis and insufficiency, and aortic insufficiency. She had received weekly parenteral organomercurial therapy (meralluride, 2 ml.) for two and a half years prior to attending the clinic. She was then placed on chlormerodrin, three tablets equivalent to 30 mg. Hg a day, for six months. At the end of that period she required only 10 mg. a day, which she continued for two years and three months. She also received prophylactic oral penicillin. She then developed symptoms and signs of bacterial endocarditis proved by blood cultures, but did not respond to treatment in spite of massive combined antibiotic therapy. The terminal clinical picture was myocardial failure.

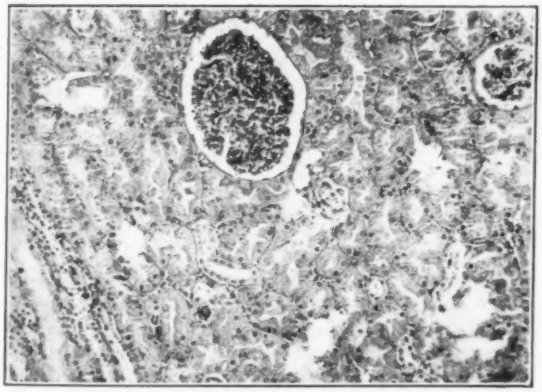


FIG. 3.—Case 16. Renal tissue shows congestion, without tubular necrosis. (×110.)

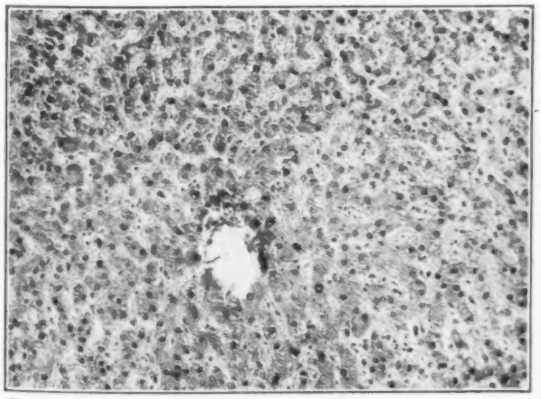


FIG. 4.—Liver of Case 16. No damage to cells. Congestion surrounding central vein, with deposits of haemosiderin. (×140.)

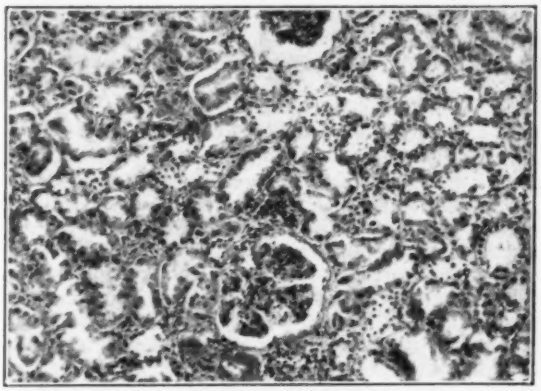


FIG. 5.—Case 11. Thickening of glomerular capsule and of tubular basement membrane, without tubular inflammation or necrosis. (×110.)

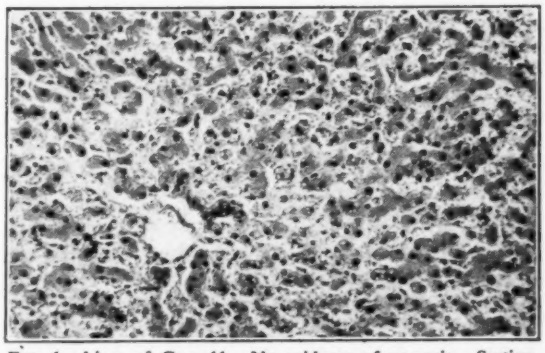


FIG. 6.—Liver of Case 11. No evidence of necrosis. Section shows congestion and oedema, with deposits of haemosiderin. (×140.)

Necropsy revealed acute and chronic endocarditis of the mitral and tricuspid valves; hypertrophy of the right and left ventricles; subacute and chronic pyelonephritis; nephrosclerosis, benign; and chronic passive congestion of the liver. Sections of the kidney showed some thickening of the capsule of the glomerulus and thickening of the basement membranes of the tubules (Fig. 5). There was no inflammation or necrosis of the tubules. Some sections showed thickening of the smaller arterioles. Sections of the liver showed congestion, oedema, and deposits of haemosiderin (Fig. 6). There was no evidence of necrosis. The patient received the equivalent of 22,600 mg. Hg as organomercurial diuretics. Her kidneys contained less than 16 mg. Hg per 100 g. of dry tissue.

It is notable in Case 11—which has the greatest concentrations among our three patients in the kidneys, liver, and large intestine (Table VI)—that no mercury was detected in the cardiac tissue. In all three cases the mercury content of the heart muscle was infinitesimal. This analysis stands in strong evidence against the direct action of mercury from organomercurial diuretics upon the heart muscle.

Thus none of our patients who came to necropsy showed evidence of any glomerular, renal tubular, hepatic, or cardiac pathology attributable to mercury.

Discussion

The lack of any renal toxicity ascribable to the diuretic in our patients corroborates early experimental results with chlormerodrin in laboratory animals. Handley, Chapman, and Moyer (1951) found that no diarrhoea, stomatitis, or other evidences of severe reaction to mercurials were sustained by dogs given chlormerodrin or meralluride, at doses several times the therapeutic level, over a period of four months. Similarly, histological studies of renal tissue from rats and guinea-pigs given massive doses of chlormerodrin revealed no significant structural changes (Fig. 7).

It is interesting to compare our analysis of human tissues for mercury with a study by Griffith *et al.* (1954). These investigators analysed the organs of 45 patients with congestive heart failure. Of the group studied, 15 had no record of having received mercury. Amounts of mercury found in their tissues are shown in the top line of Table VI. Since both young and old individuals were included in this group, it could be assumed that a trace of mercury may be found in the tissues at all ages. Therapeutically, 14 persons received less than 400 mg. of organomercurial, and 16 received 400 mg. or more. The latter group averaged 4,692 mg. The mercury content of their livers, spleens, and kidneys are shown in Table VI. Griffith *et al.* concluded that the N.P.N. values, available in 18 of the 45 patients, could not be interpreted as indicating that the amounts of mercury in the tissues of these patients were harmful. It should be noted that two-thirds of their cases involved renal disease—not of the type caused by mercurial damage or toxicity. The high N.P.N. values were consistent with the type of renal pathology.

In our own patients the amounts of organomercurial received were all in a narrow range, just above 20,000 mg. This range is roughly five times as great as the highest average of Griffiths *et al.*, and about 50 times greater than the average for their patients who received less than 400 mg. of mercury. N.P.N. values were lower in our patients than the average in their patients.

Despite the much larger amounts of organomercurial taken by our patients, the mercury content of the kidneys was less in two cases and about the same in one. For some reason, in spite of the much greater total dosage, the mercury content of the kidney of our patients was *not* proportionately higher than that of the patients of Griffiths *et al.*

Part of the difference between our results and theirs may be related to the large number of cases with renal disease, unrelated to organomercurials, in their study (Table VII). Our patient with highest kidney mercury content (Case 11) had pyelonephritis and benign nephrosclerosis. Our other two cases, both with low kidney mercury content, had no renal disease. Apparently, relatively little mercury is accumulated in the "normal" kidney of the patient with congestive heart failure. On the other hand, even where there is advanced kidney damage from other causes, as in their patients and our Case 11, only a slight increase in mercury content can be noted. The latter findings support the clinical thesis that organomercurials can be used in the presence of kidney damage so long as diuresis is constant.

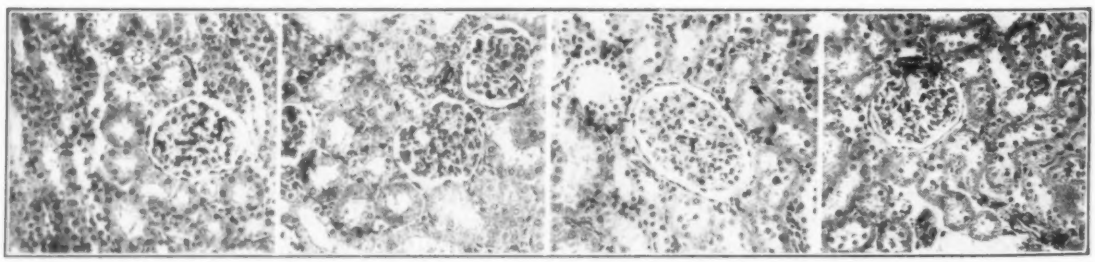
TABLE VII.—*Kidney Disease in 45 Cases (Griffiths et al., 1954)*

	15 Cases No Hg	14 Cases 400 mg. Hg or Less	16 Cases 400 mg. Hg or More
Nephrosis	2	2	2
Renal infarct	1	0	2
Pyelonephritis	0	1	2
Nephrosclerosis ..	6	6	5
Hydronephrosis	0	0	1
No disease	6	5	4

Conclusions

In our opinion, this clinical and laboratory investigation disproves the fear of an "inorganic mercury" effect from the retention of massive cumulative doses of parenteral and oral organomercurials. If there was a splitting off of inorganic mercury ions from the large amounts of organomercurials used in this series the effect upon the kidney should have been evident clinically, histologically, and in the tissue analysis. There was no renal damage from mercury in any of these areas.

Our clinical experience with the organomercurials—meralluride and chlormerodrin—supports the concept of a "specific organic molecule" as being responsible for the diuretic action, rather than a mercury action *per se*. This concept was stressed by Saxl and Heilig (1920) in their original description of the modern use of organomercurials as diuretics. More recent authorities (Smith, 1951; Strawn *et al.*, 1956) agree that mercurials are excreted as organic compounds, and that the mercury is not split off. Goodman and Gilman



A B C D

FIG. 7.—Typical sections of renal tissue from experimental animals given chlormerodrin twice weekly. No pathological changes are seen. (A) Guinea-pig, 4 mg. Hg/kg. subcutaneously, 35 doses. (B) Guinea-pig, 6 mg. Hg/kg. orally, 35 doses. (C) Rat, 9.6 mg. Hg/kg. subcutaneously, 64 doses. (D) Rat, 20 mg. Hg/kg. orally, 72 doses. (Pathological evaluations by Francis D. Speer, Professor of Pathology, New York Medical College.) (×103.)

(1955) state: "Older evidence suggested that the mercurials were active by virtue of their release of mercuric ion (Hg^{++}). However, it is more likely that organic mercury complexes dissociate as such and act in the form of the specific organic molecule, $R\text{-}Hg^{+}$." The N.N.R. specifications for chlormerodrin explicitly state that there should be "absence of ionizable mercury and other heavy metals, as indicated by the standard sodium sulfide reaction" (Council on Pharmacy and Chemistry, 1953).

Most prejudice against organomercurial diuretics is probably ascribable to the unsupportable assumption that modern organomercurials have the same basic toxicity as such toxic inorganic mercurials as bichloride of mercury and calomel. The few early organomercurials with significant toxicity, such as "novasurol" and "esidrone," have been out of use for many years, but their memory serves to prejudice the minds of many physicians.

Because the organomercurials are the most potent diuretics, and so vital in prolonging the life of the cardiac patient, the unwarranted fear of their prolonged use must be dispelled if we are to help the cardiac patient to more years of comfortable living and employment. The absence of mercurial toxicity in our patients, who took massive total doses of organomercurials over a four-year period, should remove all fear of the use of these important therapeutic agents. It is our opinion that the organomercurial drug is itself harmless provided that the physician is master of his therapy at all times. He must be alert to signs or symptoms of allergy or sensitization to the medication. He must not permit the repeated use of the organomercurials, or any other drug as a matter of fact, when such use elicits continued allergic reaction. Most of the so-called toxic reactions reported to be due to organomercurials might have been avoided if the physician had become aware of the sensitivity symptoms.

Summary

Forty-eight clinic patients in chronic congestive heart failure were maintained in a state of cardiac compensation with the oral organomercurial chlormerodrin (neohydrin) over a four-year period. All patients received maintenance digitalis and were advised to stay on a salt-free diet.

An additional five patients treated during the four-year period had gastro-intestinal disturbances manifested by nausea, vomiting, and diarrhoea. These patients were withdrawn from the study because of their intolerance to the drug.

Of the 48 patients, 39 had previously received parenteral meralluride (mercuhydrin) from six months to ten years prior to initiation of treatment with the oral drug; the other nine had never received parenteral organomercurials prior to treatment with chlormerodrin.

Combined total dosage of oral and parenteral mercury ranged from 6,240 to 78,560 mg. per patient, with no clinical evidence of renal toxicity due to the organomercurials.

Renal function was tested in every patient by means of urinalysis and tests for urea nitrogen, N.P.N., and creatinine. Urea-clearance tests were done in 17 patients. The sole abnormalities detected were occasional albuminuria in seven.

Of the eight deaths in the series, none of which were related to toxicity of the diuretic, three came to necropsy. There was no gross or microscopical evidence of renal damage due to mercury.

Tissue analysis for mercury revealed a small mercurial content in the kidneys, and infinitesimal amounts in heart muscle, liver, spleen, and large bowel.

Chlormerodrin showed no evidence of renal toxicity over a four-year period. Most so-called "toxic reactions" to organomercurial diuretic therapy can be eliminated by proper control of therapy in sensitive patients.

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The *Handbook* of University College Hospital, London, gives information on clinical pathology, preparation of patients for surgery and various types of examination, medico-legal topics, and much else besides. It also includes some tables of normal values. The editors are Dr. T. D. Whittet, Ph.D., chief pharmacist to the hospital, and Professor M. Maizels and colleagues of the department of clinical pathology, and it is obtainable from Dr. Whittet for 10s. 6d. (postage 6d.). In addition, the hospital issues "Therapeutic Notes," which are pamphlets providing in a small compass useful information on groups of drugs. Number 1, for instance, is on haemopoietic substances; number 2 on barbiturates; number 5 on penicillin. Leaflets are also provided which give supplementary formulae to those listed in the *B.P.*, *B.P.C.*, and *B.N.F.* The *Pharmacopoeia* issued by the Hospital for Sick Children, Great Ormond Street, contains instructive therapeutic notes besides a list of 210 prescriptions for children. The notes give information in summary form on the commonly prescribed groups of drugs such as antihistamines, sulphonamides, antibiotics, analgesics, and vitamins. It is obtainable for 10s. 6d. (postage 6d.) from the secretary of the hospital.

PYLORIC STENOSIS

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Pyloric stenosis is a condition in which there is obstruction to the emptying of the stomach due to an organic lesion in the region of the pylorus. The clinical features of a consecutive series of cases in the adult have never been recorded. This lack of study of such an important condition may be due, in part, to the adequacy of standard descriptions based on clinical impression. Their inadequacy in one respect, the incidence of diarrhoea, prompted the present investigation.

Methods

Major and minor diagnostic criteria were formulated before the review was undertaken. Cases were not included in the series unless two major or one major and two minor criteria were satisfied. The major criteria were: (1) a classical history—that is, the persistent vomiting of large amounts at times when the stomach should be empty, or nearly so, usually containing recognizable residues of food eaten some hours previously or accompanied by offensive eructation; (2) the presence of visible gastric peristalsis; (3) the mean daily volume of the gastric residue* exceeding 1,000 ml. on the first or last three days on which aspiration was performed; (4) the stomach emptying by less than one-third in two hours, less than a half in three hours, or less than two-thirds in four hours, as estimated by the radiologist who performed the barium-meal examination; and (5) the finding at operation or necropsy of considerable narrowing of the lumen in the region of the pylorus.

The minor criteria were: (1) a suggestive history—that is, persistent vomiting which almost satisfied the first major criterion; (2) the presence of a gastric succussion splash; (3) mean daily gastric residues exceeding 750 ml. on the first or last three days; and (4) the presence of alkalaemia as shown by a serum alkali reserve of more than 35 mEq/l. or a serum chloride concentration of less than 85 mEq/l.

In the years 1950–5 inclusive 146 adult patients were discharged from the wards of the Central Middlesex Hospital with a diagnosis of pyloric stenosis. The records of these patients have been examined and 28 rejected because they failed to satisfy the necessary criteria. Data on the remaining 118 patients (86 men and 32 women) obtained from the hospital records have been analysed and form the basis of the present study. In no case was the site of the obstruction distal to the biliary ampulla or clearly proximal to the pylorus.

*At the Central Middlesex Hospital gastric aspiration was usually performed nightly some hours after the last meal, occasionally in the morning before breakfast, and rarely at other times to relieve distress. The volume of any vomitus has been added to that of the aspirate of the day. This is justified, as vomiting in hospital probably represented inadequate aspiration or was provoked by passage of the tube.

Aetiology

The cause of the pyloric stenosis was established by laparotomy in 115 patients, at necropsy in two, and by radiology alone in one. Benign prepyloric and pyloric ulcers were classified as duodenal because distinction was impossible, the opinions of surgeon, pathologist, and radiologist often being divided on the location of the pylorus. On this basis duodenal ulceration was the cause of stenosis in 95 instances. There were coincident gastric ulcers remote from the pylorus in only four. An actual ulcer crater was found in 83 and was described as large in 41. In four further patients, although it was not discovered at the time of operation, a crater was probably present as there was a large inflammatory mass around the duodenum. In four others only scarring was noted at the pylorus, but as they were all treated by gastro-enterostomy the duodenum was not inspected from within. In two no comment on the activity of the ulcer was recorded. One was treated medically, while in the last patient a healed duodenal ulcer and an active gastric ulcer on the lesser curve were found at necropsy.

A gastric ulcer remote from the pylorus was the cause of obstruction in seven patients. In all of these laparotomy revealed a mass of fibrous tissue extending along the lesser curve and enveloping the pylorus.

In 13 cases pyloric obstruction was due to carcinoma of the pyloric antrum. In two it was due to kinking of the duodenum which had become adherent to a chronically inflamed gall-bladder. In the remaining patient it was due to a congenital diaphragmatic constriction at the pylorus.

Symptoms

The incidence of various symptoms is shown in Fig. 1. Vomiting attributable to pyloric stenosis occurred in all but three patients, being a presenting symptom in 105 and copious in at least 60. The presence of recognizable residues of food eaten 12 or more hours previously was recorded in only 18 cases. It has been stated (Crohn, 1927; Hurst and Stewart,

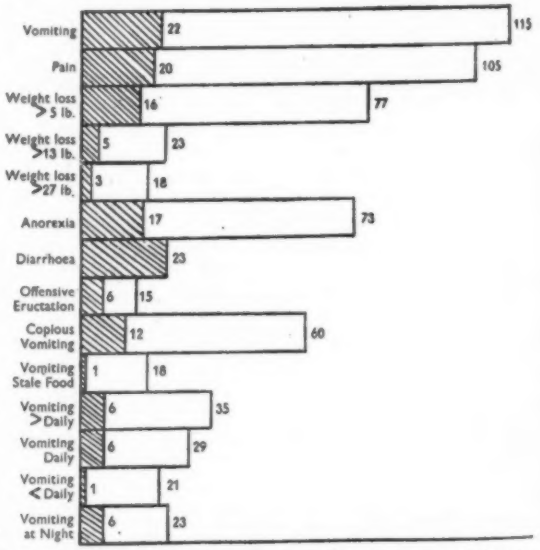

FIG. 1.—Incidence of various symptoms in pyloric stenosis due to all causes. Hatching=Cases with diarrhoea.

1929) that with increasing gastric decompensation vomiting becomes less frequent but more copious. This was observed in a minority of the patients in the present series. In some cases vomiting occurred with the same frequency throughout the illness, in some it coincided with exacerbation of ulcer pain, and in some its frequency increased. A predominant pattern was discernible in 85 cases, with daily vomiting in 29, more frequent than daily in 35, and occasional in 21.

Pain of ulcer type had occurred in 105 patients, including 90 of the 95 with duodenal ulcers. Of the latter it was severe in 31, moderate in 34, and mild in 17; no assessment of severity could be made in eight. Among the seven gastric ulcer patients pain was severe in four and mild, moderate, or indefinite in one each. Of the 13 with carcinoma, seven did not complain of pain, in three it was mild, and in three it was moderate. Both the patients with pyloric stenosis due to gall-bladder disease gave a history of ulcer-type pain.

The first symptoms (usually pain, sometimes perforation or haemorrhage) attributable to duodenal ulceration preceded admission for pyloric stenosis by 10 or more years in 53 cases and by less than five years in only 18.

Anorexia was present in 73 patients. 77 had lost 5 lb. (2.3 kg.) or more in weight. In 18 of these the loss exceeded 27 lb. (12.2 kg.) and in a further 23 it exceeded 13 lb. (5.9 kg.). Offensive eructation was noted in 15.

Diarrhoea occurred in 23 patients, excluding those with an obvious cause such as idiopathic steatorrhoea or sensitivity to antacids. In six it was severe enough to be a presenting symptom—alone in two, with vomiting in three, and with heartburn in one. In two patients there was a long-standing history of diarrhoea, starting 4 and 15 years before vomiting and relieved by partial gastrectomy. More usually there had been loose stools for a few days, sometimes alternating with bouts of constipation. The frequency of other symptoms in the 23 patients with diarrhoea was similar in most respects to that in the series as a whole, as shown in Fig. 1.

The duration of obstructive symptoms before admission to hospital is shown in Table I. It was less than one month in 37 patients, one to three months in 35, and longer than one year in only 14. The relative

TABLE I.—*Duration of Obstructive Symptoms Prior to Admission for Pyloric Stenosis*

Months:	0–	1–	3–	12+	Unknown	Total
Whole series	37	35	27	13	6	118
Cases with diarrhoea	5	12	4	1	1	23

preponderance of cases with 1–3 months' history suggesting obstruction among patients with diarrhoea is statistically of borderline significance. There does not seem to be any clear-cut explanation for this finding, which is therefore probably fortuitous.

The annual incidence of episodes of perforation and of major haemorrhage (haematemesis, melaena, or both) in the 10 years before admission for pyloric stenosis is shown in Table II. The 14 perforations (all in duodenal ulcer cases) were distributed equally between the first and second halves of this period, so that there was no marked tendency for stenosis to follow shortly after perforation. In contrast, 39 of the

TABLE II.—*Annual Incidence of Perforation and Haemorrhage in the Past Histories of All Patients in the Series, Before Admission for Pyloric Stenosis*

Year:	1	2	3	4	5	6–10*	Total
Cases of haemorrhage	22	5	4	4	4	1·4	46
,, ,, perforation ..	4	3				1·4	14

* Annual mean for the sixth to tenth years.

46 instances of major haemorrhage occurred within five years of the date of entry into hospital, 22 of them within one year.

Signs

The incidence of the three signs mainly associated with pyloric stenosis is shown in Fig. 2. A gastric succussion splash was noted in 66 of the 118 patients and visible gastric peristalsis in 33. Obvious dehydration was less common, being noted in only 29. The diagnosis of pyloric stenosis was often made in the absence of confirmatory physical signs.

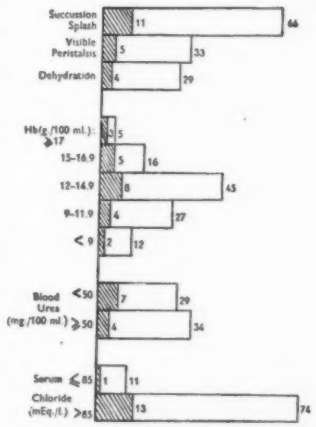

FIG. 2.—Incidence of abnormal physical signs and results of blood investigations in the whole series. Hatching=Cases with diarrhoea.

Radiology and Blood Investigations

A barium-meal examination was performed in 93 of the 118 cases and showed evidence of delayed emptying in 79. Anaemia was common and a raised haemoglobin level rare (Fig. 2). In 45 of the 105 patients tested the haemoglobin level was between 12 and 14.9 g. per 100 ml., in 27 between 9 and 11.9 g. per 100 ml., and in 12 less than 9 g. per 100 ml. Levels of 15 to 16.9 per 100 ml. occurred in 16 patients and higher levels in only five.

The blood urea was raised to 50 mg. per 100 ml. or more in about half the cases tested (34 of 63, Fig. 2). The serum bicarbonate level was estimated in only 33; in 27 it was 30 mEq/l. or higher. The serum chloride level was rarely depressed.

Age and Sex Distribution

The number of patients in different age and diagnostic groups is shown in Table III. Only 14 patients were under 40, and 63 were between 40 and 59. This pattern reflects that of the duodenal ulcer cases because of their numerical preponderance, as does the sex distribution, approximately three males to one female (Table IV). The numbers in the other diagnostic groups are too small for separate analysis.

TABLE III.—*Age Distribution in Diagnostic Groups*

Age (Years):	0–39	40–49	50–59	60–69	70+	Total
Duodenal ulcer ..	13	27	28	14	13	95
Gastric ,, ..	1	0	2	3	1	7
Carcinoma ..	0	3	2	3	5	13
Other	0	1	0	0	2	3
Total ..	14	31	32	20	21	118

TABLE IV.—*Sex Distribution of Patients in the Different Aetiological Groups*

	Whole Series		Cases with Diarrhoea	
	Male	Female	Male	Female
Duodenal ulcer ..	72	23	17	5
Gastric ,, ..	6	1		1
Carcinoma ..	8	5		
Other		3		

Diagnosis

Exactly half the patients were first seen in the out-patient department, and the presence of pyloric stenosis was recognized before admission to hospital in most of these. In 11 of the other 59, admitted as emergencies, the provisional diagnosis referred only to the underlying lesion, no special significance being attached to the vomiting. In a further seven an initial diagnosis of major haematemesis was probably incorrect, because the haemoglobin level remained normal and there was no melaena. In three of these obstruction was not suspected, while in the other four both conditions were diagnosed. Pyloric stenosis was diagnosed on admission in the remaining 41. In six of these the additional diagnosis of haematemesis was made and may have been correct.

In most respects, patients in different aetiological groups presented with similar symptoms, physical signs, and laboratory findings. The nature of the underlying lesion, when not already known, was established by radiology or laparotomy. One of the few features of value in the clinical diagnosis of malignancy was the length of time from the first symptom suggestive of peptic ulceration. Of the 14 patients in whom this did not exceed one year, nine had carcinoma. The other four with carcinoma gave histories of dyspepsia of up to 12 years' duration. In none of these had obstructive symptoms been present for more than a year. In one patient the presence of a palpable mass in the epigastrium established the diagnosis of carcinoma.

It was anticipated that the volume of the gastric residue would tend to decrease from day to day on in-patient medical treatment, including gastric aspiration or lavage, and that exceptions would indicate malignancy. This was not borne out by our findings. The volume of the aspirate on the first three days after admission and the last three before operation could be compared in 67 patients. In 22 there was an increase of between 250 and 1,000 ml. a day; the underlying lesion was cancerous in only four of these. An increase of more than 1,000 ml. a day was found in six, of whom only one had a carcinoma.

Treatment

Duodenal Ulcer Patients.—Of the 95 patients with pyloric stenosis due to duodenal ulcer, 88* were treated by surgery during their first admission for obstruction. Partial gastrectomy was performed in 68 with only one post-operative death. Twenty, mostly elderly or very ill, were treated by gastro-enterostomy, again with one death. Four were treated medically—that is, bed rest, nightly gastric aspiration, and milk feeds. Three of these required operative relief of their obstruction within nine months. The remaining three died before surgical relief was possible.

*Three had been treated medically in the Central Middlesex Hospital before 1950.

Gastric Ulcer Patients.—Of the seven patients in this group, four were treated by partial gastrectomy. One died before operation was possible. Two were treated medically; one required partial gastrectomy after three years and the other was moribund from emphysema two years later.

Carcinoma Patients.—At the first admission for pyloric stenosis due to carcinoma, total gastrectomy was performed in two patients, and partial gastrectomy in three. Gastro-enterostomy was the only operation possible in six. There was one post-operative death in each group. One patient, thought to have a duodenal ulcer, was treated medically at the first admission. Carcinoma was an unexpected finding at partial gastrectomy eight months later. The remaining patient was never fit for surgery.

Other Conditions.—In both the patients in whom adhesion to a chronically inflamed gall-bladder had caused pyloric stenosis it was possible to free the duodenum surgically: one made an excellent recovery, one died from cerebral thrombosis after operation. The congenital diaphragmatic constriction was not detected at laparotomy and was diagnosed at necropsy following fatal pulmonary embolism.

Discussion

Obstruction to gastric emptying near but not necessarily at the pylorus was the common feature of the patients in this series. By definition all had pyloric stenosis. This use of the term, although anatomically inexact, is both customary and logical, for the precise position of the stenosis does not affect the clinical management of the case, nor can it always be determined. Narrowing in this region is of importance only if it impairs gastric emptying, and the criteria of stenosis used in the present study were not satisfied unless this disturbance of function was present. The criteria being stringent, the diagnosis was reasonably certain when these were satisfied. This implies the exclusion of patients with pyloric stenosis of slight degree to whom our conclusions may not apply. Probably some others were excluded because the available data were incomplete. All those accepted had an organic lesion in the vicinity of the pylorus.

During the period covered by the present series an average of 17 patients with pyloric stenosis due to benign ulceration were seen each year at the Central Middlesex Hospital. Avery Jones and Pollak (1945) have calculated from the hospital statistics for 1943–4 that at least 500 cases of peptic ulceration per annum occur in the population served by that hospital. This figure is almost certainly too low for the period covered by the present series. It follows that less than 3.4% of peptic ulcer subjects ultimately develop pyloric stenosis of a severity sufficient to satisfy our criteria. The true rate may be in the region of 2%. Similar calculations for duodenal and gastric ulcers separately give a maximal possible incidence of 4.5% and 0.7% respectively. These rates are lower than would be found if the disease were allowed to run its natural course. Early elective surgery has removed some potential cases of obstruction from the population at risk.

In 5,000 consecutive necropsies at Leeds, Hurst and Stewart (1929) found peptic ulceration in 403, of which 63 (15.6%) had pyloric stenosis. The discrepancy between this incidence and that calculated on the basis of the present series can hardly be explained by a higher

rate of elective surgery. Furthermore, the Leeds figures refer to the time when the mortality from pyloric stenosis was falling owing to improvements in surgical technique. Under these circumstances necropsy material would underestimate the true incidence. It is therefore probable that many of the Leeds cases did not have gastric retention of a degree that would have permitted inclusion in the present series. Hurst and Stewart stated, and we confirm, that clinical cases of pyloric stenosis usually have active ulcers. That the lesions had healed in half their necropsy cases confirms that these included many examples of narrowing without obstruction.

In accordance with modern practice (Illingworth *et al.*, 1944) all ulcers have been classified as duodenal except those clearly in the stomach and separate from the pylorus. In the seven instances of stenosis due to gastric ulcer the obstruction was at the pylorus and therefore remote from the causative lesion. Considerable shortening of the lesser curve was invariably present. On the radiograph it appeared as though obstruction had been caused by kinking of the pylorus, but at operation this was always seen to be involved in extensive inflammatory fibrosis. Six of the seven patients were men. Hinds and Kemp Harper (1952) reported 10 similar cases, all in men, and attributed vomiting, which occurred in nine, to stagnation in the pouch formed by the inferior portion of the stomach. The contrast in behaviour of gastric ulcer in the two sexes is striking. Pyloric stenosis from this cause occurs predominantly in men and hour-glass constriction in women.

Coincident gastric ulcers occurred in four (4.2%) of the duodenal ulcer cases. They were found in 16 (6.7%) of a comparable series of 240 consecutive patients on whom operations for duodenal ulcer without stenosis were performed at the Central Middlesex Hospital in the years 1955–6. These figures do not support the contention of Daintree Johnson (1955) and of Dragstedt (1956, 1958) that gastric retention favours the development of gastric ulceration.

The relative importance of cicatricial narrowing, inflammatory swelling around an active ulcer, spasm, and impaired motility in the production of pyloric obstruction associated with peptic ulceration has been the subject of much speculation. Hurst and Stewart's (1929) statement that active ulceration is almost always present in clinical pyloric stenosis is confirmed by our observations. Therefore cicatricial narrowing is not a sufficient cause of gastric retention and some additional factor associated with active ulceration is necessary. Berkman (1923) reported that no obstruction was found at operation in 58.3% of patients with pyloric stenosis caused by peptic ulceration. By contrast, 12.5% of 564 ulcer cases without gastric retention had a narrowed pylorus at operation. He concluded that constriction is of no importance so long as the motor function of the stomach remains adequate. Illingworth (1953) also considered that stenosis due to scarring alone was uncommon and that spasm usually played a part, especially in cases with gastric ulcer. The high incidence of very large ulcers found in the Central Middlesex Hospital series suggests that inflammatory swelling is of importance in the production of pyloric stenosis.

The frequency of chronic perforation of duodenal ulcers in cases with pyloric stenosis has been stressed by Berkman (1921, 1923). This point was not investigated in the present series. Contrary to Crohn's (1927) view, our evidence does not suggest that acute perforation is an important factor, for its incidence was no higher in the years just before admission to hospital for pyloric stenosis than it had been some years previously (Table II).

Vomiting was the commonest symptom, and usually was copious. There was rarely a definite history of the vomitus having contained residue of food eaten 12 or more hours previously. Pain of ulcer type was a complaint in all but 5 of the 102 patients with benign peptic ulcer, and often was severe. We have not confirmed the opinion sometimes expressed (Berkman, 1923; Hurst and Stewart, 1929; Bockus, 1943; Illingworth, 1953) that the onset of pyloric stenosis is usually marked by loss of the normal periodicity of symptoms. Our evidence on this point, however, is not entirely satisfactory.

Bockus (1943), Hurst (1946), and others have stated that constipation, often severe, is invariable in pyloric stenosis. Crohn (1927) described the occasional occurrence of diarrhoea. In the present series there were 23 patients in whom diarrhoea was attributable to pyloric stenosis. It was usually slight, but in six it was severe enough to be a presenting symptom. The high incidence of offensive eructation in the diarrhoea cases, although statistically of only borderline significance, suggests that stale food in the stomach leads to the production of some substance irritant to the intestine. In other respects the findings in the diarrhoea cases do not differ substantially from those in the series as a whole. In particular the similarity of the haemoglobin, blood urea, and chloride levels (Fig. 2) suggests that neither haemorrhage nor electrolyte imbalance plays a part in producing the bowel disturbance.

Our findings on the frequency of specific physical signs agree with the views of Parsons and Watkinson (1954). A gastric succussion splash was found in about half the patients, while visible gastric peristalsis and obvious dehydration were each reported in about a quarter.

The relationship between radiological and other evidence of delayed gastric emptying has been studied by Bockus (1943) and Illingworth (1953). In general the correlation is good, but there are discrepancies in mild cases. In the present series barium-meal examination after the onset of symptoms of pyloric stenosis failed to show evidence of delayed gastric emptying in one-seventh of the cases.

Bockus (1943) comments on the frequency of anaemia in pyloric stenosis, and our findings confirm this. The blood-urea level was raised in over half the patients in whom it was estimated. This suggests that metabolic disturbance due to water and electrolyte deficiency was common.

Difficulties in diagnosis were encountered in one-third of the emergency admission cases. In particular a mistaken diagnosis of major haematemesis was made on seven occasions when the vomiting of brown fluid, subsequently shown to be due to pyloric stenosis, was described in the account of the events leading to admission. Similar errors could explain the sharp rise in the apparent incidence of haematemesis in the years immediately before the diagnosis of gastric retention (Table II).

One clinical factor analysed in this series was found to be of some value in detecting underlying cancer. If

the first symptom of gastro-duodenal disease occurred less than a year before admission for pyloric stenosis there was an almost even chance of malignancy. Bockus (1943) records similar findings. Neither the length of obstructive history nor the failure of regular aspiration to reduce the volume of the gastric residue was of value. A history of previous ulcer dyspepsia of some years' standing did not preclude carcinoma. As surgery is the only certain remedy for pyloric stenosis, whatever the cause, this clinical differentiation is not of great importance.

In the present series medical treatment, with repeated gastric aspiration or lavage, replacement of fluid and electrolyte loss, bed rest and frequent milk feeds, although an essential preliminary to surgery, was rarely tried as definitive therapy and never proved of lasting value. Emery and Monroe (1935) found benefit from such measures in 38.6% of their cases but gave no precise definition or data on length of observation after treatment. Bockus (1943) stated that 50% of patients improved by medical measures would relapse and need operative relief of their obstruction. In view of the low mortality associated with modern surgery, other definitive measures have been largely superseded. There were only two deaths in the present series among 92 patients treated surgically for pyloric stenosis due to benign ulceration. By contrast, only 4 of the 13 with carcinoma left hospital after a potentially curative operation.

Summary

A precise definition of pyloric stenosis, and the diagnostic criteria, are given. The clinical, radiological, laboratory, and morbid anatomical findings in 118 consecutive cases of pyloric stenosis are reviewed. Active duodenal ulceration was the commonest cause.

Diarrhoea attributable to pyloric stenosis was found in 20% of the patients in the series. Its causation is discussed. In other respects previous descriptions of pyloric stenosis have, in general, been confirmed.

The definitive treatment was surgical in nearly all cases.

We thank Drs. F. Avery Jones and W. R. S. Doll for encouragement, helpful criticism, and advice in the preparation of this report. We are grateful to the other members of the staff of the Central Middlesex Hospital for permission to study the cases admitted under their care. We are indebted to Miss Barbara White, who performed the statistical analyses.

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CHLOROQUINE PER RECTUM FOR MALARIA IN CHILDREN

BY

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The use of chloroquine in suppositories for the treatment of malaria in children was introduced seven years ago in to-day's Vietnam by Canet (1951). This method, advocated by Lavier and Schneider (1951), has subsequently been quite widely adopted in paediatric practice in French overseas territories. Nevertheless it is little known or used in other countries, and was not mentioned in the comprehensive monograph on chemotherapy of malaria by Covell, Coatney, Field, and Singh (1953).

As problems connected with treatment of malaria in children were recently reviewed by one of us in preparing a chapter on malaria for Trowell and Jelliffe's (1958) book on tropical paediatrics, it was proposed to assess the value of rectal administration of chloroquine on a selected group of hospitalized African children. We thought it would be of interest to evaluate not only the comparative parasiticidal action of the drug given per rectum or by mouth, but also to determine the respective rates of urinary excretion of the chloroquine base.

Material and Technique

The trial was carried out in the children's ward of the Royal Orthopaedic Hospital at Igbobi, near Lagos. Twenty-eight children who were admitted for various bone and joint diseases but who, on admission, were found to be also infected with malaria were selected for the trial. After a preliminary screening, the children, whose mean age was 6.8 years, were divided into two groups. One group of 10 received chloroquine sulphate by mouth in one single dose containing 300 mg. of chloroquine base. The other group, composed of 18 children, was subdivided, so that one subgroup comprising 12 children was given a single chloroquine sulphate suppository containing 300 mg. of base, while the other subgroup, consisting of six children, had one such suppository every day for five days, thus receiving a total dose of 1,500 mg. of chloroquine base.

All the children were on the same hospital diet, but the fluid intake was not controlled. The drugs were given personally by one of us, and thick blood films were taken daily for one week after the administration of chloroquine. The slides, stained with Giemsa, were examined for the presence of malaria parasites, their species, and the parasite density. The percentage of daily slides cleared of malaria parasites and the "clearance time" were used as an indication of the activity of the drug administered to each group. This method has been used for several similar investigations (Bruce-Chwatt, 1951; Bruce-Chwatt and Archibald, 1953; Bruce-Chwatt and Charles, 1957), and need not be described in detail.

The rate of absorption and excretion of the antimalarial was estimated from the amount of chloroquine base eliminated in daily samples of 24-hour urine during

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one or two weeks following the administration of the drug. The method used for chloroquine estimation in the urine was that of Fuhrmann (1950), which measures the turbidity produced in the acid solution of extracted chloroquine base after the addition of the Mayer–Tanret reagent. The original method was slightly modified so that only 100 ml. of urine was necessary.

The turbidity was measured in a Spekker H760 absorptiometer, using a 508 filter. The amount of chloroquine in the solution was estimated from a calibration curve prepared from known amounts of chloroquine sulphate. The value of this method was previously assessed by Charles (unpublished report). We found that blank readings on normal urine gave no turbidity or at most only an opalescence below the threshold value of the calibration curve. The reliable quantitative sensitivity threshold of this method was estimated at 0.1 mg. of chloroquine per 100 ml. of urine.

Results of the Investigation

As usual in Southern Nigeria, the predominant parasite species was *Plasmodium falciparum*, which occurred in all children of the positive selected sample. *P. malariae* in association with *P. falciparum* occurred in 14% of the children. The overall parasite density index was 4.2 and centred around 800–1,600 parasites per c.mm. Gametocytes of *P. falciparum* were present in 17% of cases.

Since it was important for this investigation to determine only the comparative speed of action of the three treatments, the daily blood examinations were not extended beyond the eighth day after beginning the chloroquine administration. The results are shown in the Table.

Disappearance of Parasitaemia in Three Groups of Children After Chloroquine Administration

Group	No.	Percentage Cleared Within 1 Week	Clearance Time in Days. Mean and S.E.	Gametocyte Rate for *P. falciparum* at End of Week
Single dose 300 mg. by mouth	10	100	1·8±0·2	20%
Single dose 300 mg. in one suppository	12	38	2·8±0·4	25%
1,500 mg. in 5 suppositories over 5 days	6	100	3·0±0·06	17%

In two children of the two larger groups fully grown schizonts of *P. malariae* persisted in the blood for two to three days after the *P. falciparum* infection was cleared, but the small number of these cases did not justify the calculation of a specific clearance time for *P. malariae*.

There was no significant change in the gametocyte rate of *P. falciparum* after the last day of examination, at the end of the week. Neither was there any evident correlation between the original parasite density count of individual children and their clearance time.

The comparative rates of excretion of chloroquine in urine, following the administration of a single dose given by mouth or of a single and multiple dose administered per rectum were assessed in 20 children.

It was found that after the oral administration of a single dose of chloroquine sulphate (300 mg. chloroquine base) to six children the mean amount of the base excreted in the urine of each child over eight days was 58.9 ± 4.8 mg., or 19.6% of the administered drug. Of the same amount of chloroquine sulphate (300 mg. base) given as a suppository to each of eight children, the mean recovery in the urine over eight days was 14.6 ± 3.9 mg. per child (4.9% of the administered dose). We have also administered to six children once a day over five days a suppository containing 300 mg. of chloroquine base; the mean amount of the drug recovered in the urine within two weeks after the administration was 82.0 ± 9.2 mg., or 5.5% of the total dose of 1,500 mg.

Clinical Value of Chloroquine Suppositories

The results of this study show that at the single dosage of 300 mg. of base the drug given by mouth is about three times as active as when given in the form of suppositories, the proportions of children cleared of parasites within a week after the drug administration being respectively 100/38, or a ratio of 2.6. The relevant ratio between the urinary excretion of the chloroquine administered as a single dose by the two ways is 4:1 (19.6% against 4.9%) in favour of the peroral treatment.

While a single intrarectal dose of 300 mg. of chloroquine cleared only 38% of the sample of children infected with *P. falciparum*, the multiple administration of 300 mg. of the drug daily for five days cleared all the children of our sample within one week. It appears that the intrarectal absorption of the drug when given in multiple doses is of greater therapeutic value. As pointed out by Canet (1951), when it comes to speed of action the intrarectal administration of chloroquine for treatment of severe malaria cannot compete with the oral, let alone parenteral, administration of the drug. Nevertheless, there might be circumstances when chloroquine suppositories would be of value if the taking of the drug by mouth presented difficulties, as might often be the case in paediatric practice. Vomiting and refusal to swallow the tablet are the most common indications for intrarectal treatment of not too severe malaria, perhaps after a preliminary parenteral loading dose. It is obvious that chloroquine suppositories must be given in much higher dosage than when the drug is given by mouth.

Canet (1951) advised that the intrarectal dose should be approximately twice the oral dosage. With a dose of 750 mg. (to children under 3 years of age) and of 1,350 mg. (to children of a mean age of 7 years) given over three days, Canet noted the disappearance of parasitaemia (*P. falciparum* and *P. vivax*) in all his 40 Vietnamese children. The mean clearance time of his series of *P. falciparum* infections was 2.85 days. The results obtained by us with a smaller sample of slightly older African children, given 1,500 mg. of intrarectal chloroquine over five days, were very similar, the mean clearance time being 3.0 days. Canet thought that the total dosage of chloroquine in suppositories given over five days should be as follows: infants, 750 mg.; 1 to 3 years, 1,050 mg.; 3 to 6 years, 1,800 mg.; 6 to 10 years, 2,400 mg. These dosages are actually more than twice the generally accepted oral dosage (Covell *et al.*, 1953), but, judging from the comparative rates of chloroquine excretion, are perfectly acceptable. In fact, it seems that at times even a higher intrarectal dosage of chloroquine might be justified, especially as side-effects of this treatment have not been recorded and are probably very rare.

A point should be mentioned with regard to the technique of intrarectal administration of chloroquine. The available suppositories are of two strengths—300 and 150 mg. of chloroquine base; they are very well preserved in a plastic strip pack, but have the disadvantage of getting soft in tropical climates and

must be kept on ice before use. This might not always be easy, and it seems that suppositories with a higher melting-point would be desirable for tropical practice.

The French workers believe that chloroquine suppositories might have some use not only for treatment but also for prevention of malaria in infants and small children at a weekly dosage of 150 to 600 mg. (one or two suppositories a week). That this is a possibility cannot be denied, though the value of this method is surely limited to exceptional cases.

Intrarectal chloroquine might be of value in the treatment of amoebiasis, rheumatoid arthritis, and lupus erythematosus.

Urinary Elimination of Chloroquine

Comparing the renal elimination of a single dose of chloroquine given by mouth with that given per rectum, it was of interest to find that the trend of the daily excretion of the drug is similar and that the amount of chloroquine base found in the urine 24 hours after administration decreased in both groups to one-tenth of this value in about six days. The excretion curve of chloroquine after repeated daily administration of five suppositories showed a slight peak on the fourth and fifth days, but maintained its relatively uniform level for one week. The proportion of the total amount of chloroquine excreted within two weeks after five suppositories was slightly higher (5.5%) than in the case of a single dose (4.9%).

It must be made clear that this investigation gives no direct information on the actual chloroquine concentration in the plasma of our patients. Renal excretion of many synthetic antimalarials depends on so many variables (in addition to plasma concentration) that it cannot be used for direct estimation of the amount of the drug in body fluids or tissues.

Haag, Larson, and Schwartz (1943) showed that the amount of quinine eliminated in the urine depends on the acid-base balance of the individual. The Army Malaria Research Unit, Oxford (1945), found that the same is true with regard to mepacrine, and that the excretion of this drug by the kidneys is correlated with the excretion of ammonia and with plasma mepacrine concentration. The latter finding led to an elegant method of indirect calculation of plasma mepacrine levels from two empirical formulae based on the fact that the ratio of urinary mepacrine to urinary ammonia is proportional to the plasma mepacrine concentration.

The influence of the acid-base balance on the urinary elimination of chloroquine was studied by Jailer *et al.* (1947), who found that the daily excretion of the drug averaged 24% of the daily dose. Administration of sodium bicarbonate for three days decreased the mean daily excretion rate of chloroquine to 12.8%, while acidification, using ammonium chloride, increased the rate to an average of 37% of the daily intake.*

In a study of the absorption and excretion of several antimalarial drugs Berliner *et al.* (1948) confirmed these findings, and reported that chloroquine was excreted in faeces in a proportion of 8% of the daily dose of the drug, while under ordinary conditions the urinary excretion averaged 14% of the daily dose (range 10–25%). Berliner and his colleagues found that the metabolic fate of chloroquine varies from man to man, but that generally about 25% of the drug is excreted, while the rest undergoes slow degradation.

In most of the chloroquine estimations carried out by the authors quoted above one or other of the specific and sensitive methods of Brodie *et al.* (1945, 1947) was used. It was therefore of interest that our investigation of the urinary excretion of chloroquine, using a non-specific and admittedly less sensitive turbidimetric method, produced very similar results. The amount of chloroquine base excreted by our first series of children was 19.6% of the administered dose. The relevant figure was 24% as found by Jailer *et al.* (1947), 14% by Berliner *et al.* (1948), and 29% by E. Paulini and R. Soarez (1956, unpublished); while Fuhrmann and Koenig (1955), who used a turbidimetric method, reported that 16.9% of the intake of the drug is excreted in the urine.

*The therapeutic implications of this finding are considerable, especially in cases where the use of high doses of chloroquine is followed by the well-known side-effects of the drug. Administration of acids will speed up the elimination of chloroquine from the body.

Summary

The parasiticidal action of chloroquine sulphate given by mouth was compared with that given per rectum, in suppositories, in three groups of hospitalized African children. It was found that the single intrarectal dose of 300 mg. (base) of the drug cleared only 38% of children of *P. falciparum* schizonts, against 100% when the same dose of chloroquine was given by mouth.

With five repeated daily doses of 300 mg. (base) the action of chloroquine suppositories was complete though slow, with a clearance time of three days.

Chloroquine given by the mouth is far better absorbed and its urinary excretion averages 20% of the total amount of administered drug; the respective figure for intrarectal chloroquine does not exceed 5%.

Chloroquine suppositories cannot replace the more usual methods of administration of this drug, especially when the speed of action is of importance. Nevertheless, they might be used with advantage in some special circumstances, particularly in paediatric practice.

A turbidimetric method of chloroquine assay in urine was used with satisfactory results.

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THE INSULIN EQUIVALENCE OF SALICYLATE

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Interest in the action of salicylate in diabetes mellitus has been revived by the observation that aspirin is capable of controlling the hyperglycaemia and glycosuria and of abolishing moderately severe ketosis in diabetes mellitus (Reid, Macdougall, and Andrews, 1957). Disadvantages of the therapy are early development of nausea and vomiting in a few patients, and the more frequent but none the less annoying side-effects of tinnitus and deafness. Nausea and vomiting are due to unsuspected overdosage with salicylate and are associated with very high serum salicylate levels. They are serious because they give rise to a starvation ketosis which is difficult to distinguish from diabetic ketosis, and this confusion probably accounts for the abandonment of salicylate in diabetes long before the introduction of insulin. Fortunately, nausea and vomiting need not arise if salicylate dosage is controlled by serum salicylate estimations in the early days of treatment, so that none of the disadvantages really presents an insuperable problem to its use in diabetes. Indeed, the fact that long and continuous administration of aspirin is not accompanied by risk of serious toxic effects such as agranulocytosis is in its favour, for while this risk may be negligible in short-term treatment it is not in a treatment which lasts for life.

The practical value of aspirin in diabetes, however, cannot be decided until its effectiveness has been compared with that of insulin, the most powerful antidiabetic agent known. In this paper the insulin equivalence of aspirin has been investigated in a group of 14 patients whose insulin requirements as out-patients ranged from 14 to 112 units each day. The amount of insulin which could be replaced by a maximal tolerated course of aspirin was determined in each patient. The patients were referred to us from the hospital diabetic clinic. Some were well controlled with insulin, but a good proportion of difficult cases who were not well controlled were included in the series. The complete practical range of insulin requirements has been covered, and it may fairly be claimed that the group represents a cross-section of diabetics who require insulin.

Clinical Particulars and Methods

Clinical particulars are shown in Table I. Ages of the patients ranged from 33 to 74 years. Nine were females, five were males. The duration of the disease varied from 1 to 24 years, the carbohydrate intake from 104 to 295 g. daily, and total calories from 1,300 to 2,700. The diets which the patients were accustomed to take as out-patients were continued throughout their whole stay in hospital—that is, for the duration of the investigation—except in one patient in whom a slight alteration was made during the insulin period. The only notable change in insulin administration apart from small adjustments in dosage was to replace protamine zinc insulin (P.Z.I.) with insulin zinc suspension (I.Z.S.) in three patients so that all received the same type of insulin. Therapy was controlled by fasting blood sugars estimated by Lehmann and Silk's (1952) modification of Folin and Wu's method and tests for glycosuria (Benedict, 1911).

TABLE I.—*Clinical Particulars*

Patient	Age and Sex	Duration of Diabetes Years	Out-patient Daily Insulin Requirement (Units)	Diet	
				g. Carb./Day	Total Cals./Day
K. L. ..	67 F	14	14 I.Z.S.	104	1,200
S. McR.	50 F	4	20 ,,	120	1,400
A. C. ..	68 M	4	20 ,,	197	2,100
S. M. ..	65 M	24	22 ,,	209	2,200
*E. J. ..	55 M	1	24 ,,	150	1,900
S. W. ..	65 F	13	28 ,,	165	1,700
J. C. ..	66 F	6	36 ,,	150	1,700
S. H. ..	74 F	7	38 P.Z.I.	104	1,400
C. McP.	67 F	6	40	198	2,000
H. McM.	58 F	7	56 I.Z.S.	130	1,500
D. L. ..	68 M	3	58	224	2,300
M. C. ..	74 F	12	60 P.Z.I.	104	1,300
R. C. ..	33 M	20	76 I.Z.S.	295	2,700
C. McR.	51 F	8	112 ,,	207	2,000

* Diet increased to 194 g. of carbohydrate a day during insulin therapy.

After an initial control period of at least 10 days during which the patients received their appropriate doses of insulin, aspirin therapy was then started and insulin therapy continued. Aspirin was administered in doses to attain maximum therapeutic serum salicylate levels of 35 to 45 mg./100 ml. to give the drug every opportunity to exert a full therapeutic effect under well-controlled conditions. Estimations of the fasting blood sugar and urinary sugar were continued and insulin dosage was reduced progressively if warranted by the biochemical findings. This procedure was followed in 12 patients: the other two were new diabetics, and they were given a course of aspirin before insulin to find out if reversing the treatments had any effect. The amount of insulin which could be replaced by maximal therapeutic doses of aspirin was thus determined for each patient.

Insulin Equivalence of Aspirin

The main findings are presented in Table II, where it will be noticed that it was possible to reduce insulin requirement of every patient after two to three weeks' treatment with aspirin.

Eight patients with an initial requirement of 12 to 48 units of I.Z.S. were able to do without insulin

TABLE II.—*Insulin Equivalence of Aspirin*

Patient	Diet Carb. (g./Day)	Without Aspirin Control Period		During Aspirin 2–3 Weeks		Difference in Insulin Requirement (Units I.Z.S./Day)
		Insulin Requirement (Units I.Z.S./Day)	Fasting Blood Sugar (mg./100 ml.)	Fasting Blood Sugar (mg./100 ml.)	Insulin Requirement (Units I.Z.S./Day)	
S. Mc R.	120	12	100	100	0	12
K. L. ..	104	14	170	100	0	14
A. C. ..	197	20	272	160	0	20
*E. J. ..	150	24	134	132	0	24
S. W. ..	165	28	214	90	0	28
*J. C. ..	150	36	150	122	0	36
S. H. ..	104	36	165	150	0	36
M. C. ..	104	48	148	95	0	48
S. M. ..	209	22	48–272	135–300	12	10
C. McP.	198	32	96–284	75–326	16	16
H. McM.	130	42	55–360	51–336	28	14
D. L. ..	224	52	52–272	40–290	40	12
R. C. ..	295	76	72–262	71–255	56	20
C. McR.	207	112	255	135	40	72

* Aspirin preceded insulin therapy.

altogether while aspirin was being given. Their fasting blood sugars at the end of the insulin and the aspirin periods were quite steady, indicating stable control with both insulin and aspirin, though the sugar levels with aspirin tended to be lower and nearer normal than with insulin.

Another five patients had a modest reduction in insulin requirement of 10 to 20 units of I.Z.S., but the lability of the fasting blood sugars during the courses of insulin and combined insulin and aspirin indicated that they were not well controlled with either treatment.

The last patient, a severe diabetic, required 112 units of I.Z.S. daily, and this was reduced by 72 units while she was receiving aspirin. Stable fasting blood sugars were observed both with insulin and with combined insulin–aspirin, but the values from the combined course were about half those from the initial insulin course, indicating an insulin equivalence of more than 72 units.

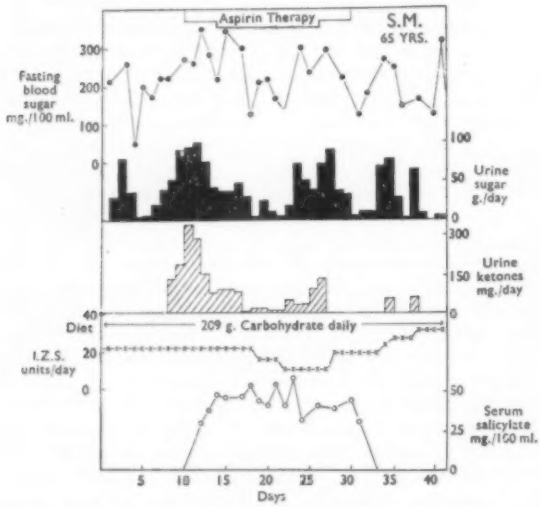

FIG. 1.—Poor response to insulin and aspirin therapy as indicated by the fluctuations in fasting blood sugar and persistence of glycosuria. The only noteworthy change was the reduction in ketonuria with aspirin.

So much for the basic results. Individual and more detailed findings from representative patients in the classes of response to aspirin just described are given below.

Patient S. M.—A male diabetic aged 65 did not respond well to aspirin. The unpredictable variations in fasting blood-sugar level and in glycosuria and ketonuria before aspirin was given indicated that he was not well controlled with insulin alone (Fig. 1). Aspirin therapy had little effect on the blood-sugar level, though just before it started and during its administration the patient had a sharp bout of diarrhoea with a slight rise of temperature. Reduction in ketonuria during the combined aspirin–insulin therapy is noteworthy, and it may be that we are being a little hard on aspirin in allowing an equivalence of only 10 units, since the patient required about 32 units of I.Z.S. after the course of aspirin to achieve comparable results, though the intercurrent infection made more precise interpretation of the results impossible.

Patient M. C.—An overweight woman aged 74 was well stabilized with insulin before the start of aspirin. Glycosuria was slight. She had no ketonuria, and her insulin requirement before aspirin was 48 units a day. It was possible during the period of aspirin therapy to reduce

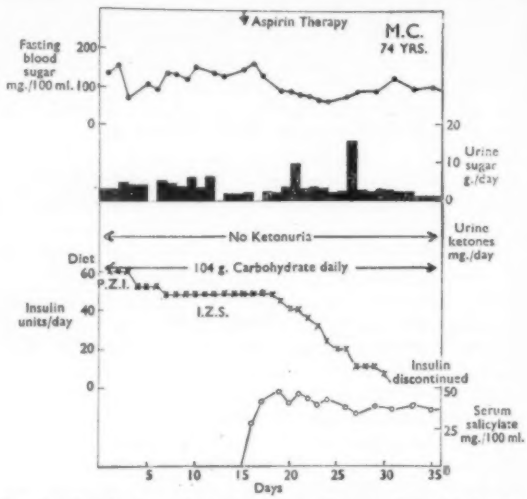

FIG. 2.—Results in patient who was well controlled with insulin and who had an excellent response to aspirin. It was possible to replace the total requirement of 48 units of I.Z.S. with aspirin.

progressively and finally discontinue insulin altogether (Fig. 2). In this patient the insulin equivalence of aspirin was some 48 units of I.Z.S.

Patient C. McR.—A fairly stable diabetic woman aged 51 required the largest dose of I.Z.S. (112 units a day). Insulin requirement in this case was reduced to 40 units a day, and this probably is an understatement, because fasting blood sugar and glycosuria were lower during aspirin therapy than they were in the control period with insulin alone (Fig. 3). The insulin equivalence was therefore more than 72 units a day.

Patient J. C.—This case shows what happens when the aspirin course precedes insulin administration. The high fasting blood sugar (240 mg./100 ml.) before aspirin administration is quickly brought under control (122 mg./100 ml.) (Fig. 4). After stopping aspirin the blood sugar takes just about as long to reach the pre-aspirin level as it took to come down to normal. Insulin therapy was then

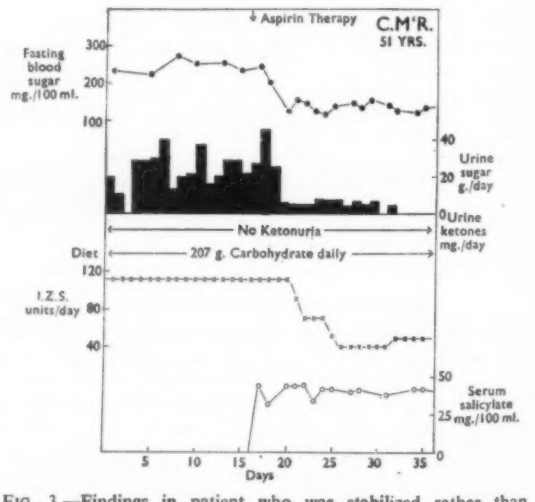

FIG. 3.—Findings in patient who was stabilized rather than controlled with 112 units of I.Z.S. The main effects of aspirin were a fall in fasting blood sugar to normal and diminution in glycosuria, accompanied by a reduction in insulin requirement to 40 units daily.

started, and 36 units of I.Z.S. a day were required to maintain the fasting blood sugar at a slightly higher control level. The findings in this patient and similar observations in the other patient in whom aspirin came before insulin suggest that the order of treatment does not affect the results.

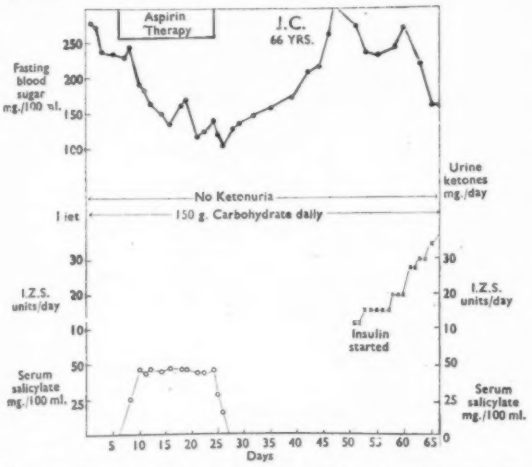

FIG. 4.—Course of events when aspirin therapy precedes insulin. Fasting blood sugar returns to normal during aspirin administration only to revert to diabetic levels after stopping the drug. Thirty-six units of insulin were required to bring the fasting blood-sugar level back to a slightly higher control level than with aspirin.

Dose of Aspirin and Serum Salicylate Levels

The serum salicylate levels, estimated by Trinder's (1954) method, which produced these antidiabetic effects are shown in Table III together with the doses of aspirin required and the body weights of the patients. The mean levels ranged from 37 to 47 mg./100 ml. and there was no obvious correlation between body weight, dose, and the serum concentration of the drug. The dose of aspirin required by each patient to attain a particular serum salicylate level was fairly constant for the individual, though some patients required twice the dose of others to achieve the same level of the drug. This is why it is so necessary to estimate serum salicylate levels to find out the precise dose required by each individual to control diabetes mellitus.

TABLE III.—*Dose of Aspirin and Serum Salicylate Level*

Patient	Weight (kg.)	Maintenance Dose Given 5 Times Daily		Serum Salicylate Level (mg./100 ml.)	
		gr.	g.	Range	Mean
S. McR. ..	67·6	20	1·3	34–53	42
K. L. ..	64·4	17½	1·2	38–44	41
A. C. ..	65·5	22½	1·5	35–51	41
E. J. ..	64·8	22½	1·5	40–52	45
S. W. ..	67.5	10	0·7	37–56	47
J. C. ..	63·8	17½	1·2	39–44	41
S. H. ..	79·9	17½	1·2	40–45	43
M. C. ..	76·6	12½	0·8	35–48	40
S. M. ..	47·6	17½	1·2	35–58	47
C. McP. ..	54·4	17½	1·2	35–45	39
H. McM. ..	73·0	22½	1·5	31–43	37
D. L. ..	78·5	17½	1·2	36–52	41
R. C. ..	59·1	22½	1·5	37–46	44
C. McR. ..	50·3	17½	1·2	35–46	42

Toxic Effects from Aspirin

The full course of aspirin gave rise, as expected, to undesirable effects. These were of two kinds: firstly, serious but transient effects due to overdosage with aspirin in the early days of treatment; and, secondly less serious but nevertheless annoying symptoms of tinnitus and deafness. The transient but serious symptoms of anorexia and nausea developed in seven patients and went on to vomiting in one patient. These symptoms were controlled by reducing aspirin dosage and lowering serum salicylate level. The "special salicylate syndrome" of mental confusion, dehydration, and hyperventilation associated with a respiratory alkalosis (Reid, Watson, and Sproull, 1950) was encountered in mild form in one patient. This syndrome is associated with intensive metabolic stimulation from overdosage with salicylate, and all its signs and symptoms disappear when salicylate has been discontinued.

During salicylate therapy 12 of the 14 patients noticed varying degrees of impaired hearing, which reverted to normal after the drug was discontinued. Seven patients developed tinnitus, which, however, tended to disappear spontaneously as time went on.

These toxic effects from aspirin, particularly the early transient symptoms due to overdosage with the drug, present a real problem, and they will have to be avoided if aspirin is to find a place in treatment of diabetes. Control of therapy by dosage alone without reference to the serum level of the drug is not, in our view, feasible, because of the wide individual difference in dosage required to produce the same blood level (Table III). It is therefore necessary in the early stages to control therapy by serum salicylate estimations. After the dose has been found for each patient, which gives the desired serum level of the drug for effective control of diabetes, the estimations may be discontinued.

Discussion

Aspirin in full therapeutic doses is not so effective as insulin. The greatest amount of I.Z.S. which could be replaced by aspirin was more than 72 units a day, and this in the patient with the greatest insulin requirement. The maximum requirement which could be completely replaced by aspirin was 48 units a day, but responses like these were obtained only in patients who were well controlled with I.Z.S. alone. Patients who were difficult to control with I.Z.S. were equally difficult to control with aspirin. Another point worth mentioning is that the increasing response to aspirin as insulin requirement becomes greater suggests that the frequency of hypoglycaemic attacks in patients requiring large daily quantities of insulin may be reduced by combined aspirin–insulin therapy, and the fact that hypoglycaemia is not a feature of aspirin therapy may have a bearing on this.

These results place salicylate in the class of promising compounds for oral treatment of diabetes and justify carrying on investigations, firstly, to try to overcome the disadvantages of salicylate therapy already referred to; and, secondly, to find out how it acts. We are investigating the possibility of freeing salicylate from its undesirable side-effects, and Manchester, Randle, and Smith (1958) have observed that salicylate, like insulin, increases glucose uptake by isolated rat diaphragm. Unlike insulin, however, salicylate increases the potassium loss and diminishes the amino-acid incorporation in protein, and it is not without interest that these biochemical observations on isolated muscle agree in general with the changes from salicylate we have observed in rheumatic patients (Reid *et al.*, 1950).

Summary

The insulin equivalence of aspirin has been determined in 14 diabetics with insulin requirements of 12 to 112 units of insulin zinc suspension daily.

Nine patients, who were well controlled with insulin, also had good responses to aspirin. The largest quantity of I.Z.S. replaced completely with aspirin was 48 units; the largest reduction in insulin requirement was 72 units in the patient receiving 112 units daily.

Five patients who were poorly controlled with insulin were not materially improved by aspirin therapy. It was concluded that aspirin was most effective in patients who responded well to insulin, and vice versa. The findings in patients well stabilized with insulin also suggested that the higher the insulin requirement the greater was the amount of hormone that may be replaced by aspirin.

These results place salicylate in the class of promising oral antidiabetic substances, and should stimulate investigations to remove its undesirable effects and to find out how it acts.

Our thanks are due to Miss M. McCombie, of the dietetic department of the Western Infirmary, for supervision of the diets, and to the staff of the unit for invaluable technical assistance.

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RESPIRATORY VIRUS INFECTIONS IN THE GLASGOW AREA

BY

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This paper summarizes further investigations of acute respiratory illnesses during two years after the period dealt with in a previous report (Grist *et al.*, 1957). In addition to observations during the epidemic of Asian influenza, further evidence was found of infections with adenoviruses and with agents related to the Sendai virus (Kuroya *et al.*, 1953).

Materials and Methods

Over 1,000 cases were investigated during the period July, 1956, to April, 1958. Most of these were patients admitted to adult and baby pneumonia wards; over 200 were adult cases seen in general practice (Blair *et al.*, 1959). Serological tests of paired sera were made in most cases, but virus isolation was attempted with necropsy material from 32 cases and with throat swabs, garglings, or stools from a number of other cases in hospital, general practice, or seen by public health officers.

Technical methods have been described previously (Grist *et al.*, 1957). So far as was possible, haemagglutination inhibition (H.I.) tests with Asian (A/Singapore/4/57), A-prime (A/Scotland/1/53), and A/PR8 influenza virus were performed in addition to routine complement-fixation (C.F.) tests on sera collected after February, 1957.

Adenovirus Investigations

Rising C.F. antibody titres were shown by 10 patients whose main features are summarized in Table I. Most of these patients had respiratory illnesses, but Case 2 presented gingivo-stomatitis with ulceration of tongue and exudative tonsillitis, enlarged tender cervical and axillary lymph nodes, and palpable spleen. The blood showed leucocytosis of 15,000 per c.mm., with 65% lymphocytes. The Paul–Bunnell test was negative on three occasions. The throat swab contained normal mixed bacterial flora. The illness did not respond to penicillin, but resolved slowly over a fortnight. Neutralization tests showed no antibodies to adenovirus types other than type 2, which gave titres of 8 and 16 in consecutive sera. A monotypic type 2 adenovirus response was also given by Case 3 (N.T. titres <8 and 32). Neutralizing antibodies to several adenovirus types were developed by three adults tested, the major responses being to type 7 (Case 7), type 2 (Case 9), types 2 and 3 (Case 10). Type 3 adenovirus was isolated from Case 3.

TABLE I.—*Cases With Evidence of Adenovirus Infection*

No.	Age (Years)	Clinical Features	Adenovirus C.F. Titres	
			"Acute" Serum	"Convalescent" Serum
1	<1	Bronchitis	<2	8
2*	2	"Glandular fever"	<8	32
3*	3	Pneumonia	32	128
4	3	"	<4	8
5†	3	Tonsillitis	8	64
6	5	Bronchitis	<2	8
7	28	Rhinitis	<2	16
8	45	Pharyngitis	<2	16
9	54	"Influenza"	<2	16
10	61	Pharyngoconjunctivitis	8	32

* Monotypic type 2 neutralizing antibody response.
† Type 3 adenovirus isolated from stool.

Sendai Virus Investigations

Serological tests showed rising C.F. titres in 10 cases whose main features are summarized in Table II. In view of the reported antigenic overlap between Sendai and mumps viruses, sera from these cases were also tested with mumps antigens where possible. The results, summarized in Table III, show various combinations of reactions. Two Cases (Nos. 12 and 19) showed increasing titres of mumps antibody, which in Case 19 were confined to the "V" antigen.

TABLE II.—*Cases With Serological Response to Sendai Virus*

No.	Age (Years)	Clinical Features	Sendai C.F. Titres		
			"Acute" Serum	Second Serum	Third† Serum
11	1	Bronchitis	<2	16	16
12*	2	Pneumonia	<4	8	16
13	4	"	<8	32	—
14	7	"	<4	8	—
15	20+	"Influenza"	<8	16	—
16*	20+	Febrile catarrh	16	64	—
17	31	Pneumonia	<8	16	8
18	49	"	<4	16	8
19*	55	"	4	64	—
20*	78	"	<8	64	—

* Also tested for mumps (Table III).
† Taken in 5th week after onset of illness.

TABLE III.—*Cases Tested With Mumps and Sendai Antigens*

No.	Age (Years)	Day of Illness when Serum Taken	C.F. Titres with Indicated Antigens		
			Sendai	Mumps "S"	Mumps "V"
12	2	6	<4	—	—
		16	8	<4	<4
		32	16	16	16
16	20+	?	16	8	8
		?+22	64	8	8
19	55	14	4	<4	4
		27	64	<4	32
20	78	3	<8	—	—
		13	64	<4	<4

Influenza Virus Investigations

During the whole period no type B and only one type C infection was detected. No outbreak of influenza was experienced during the winter of 1956–7, and serological evidence of type A infection before the Asian outbreak was limited to one case in October, 1956, and 13 in the period March–May, 1957. No strains of virus were isolated during this period, but H.I. tests showed antibody responses predominantly to A-prime virus. The main Asian influenza epidemic occurred during August–October, 1957, with a minor second wave of infection in January–March, 1958 (Horne, 1957; Grist, 1958a, 1958b). A comparison of these two waves of influenza will be reported separately (Grist, to be published). Sixteen strains of virus were isolated during the first wave and 10 during the second, 12 from post-mortem lung specimens. Serological tests by Dr. A. Isaacs at the World Influenza Centre, and cross-H.I. tests performed in this laboratory, using antisera from fowls immunized by serial intraperitoneal injections, showed no evidence of antigenic variation during the outbreak.

Six cases of suspected influenzal encephalitis were examined: three adults showed no laboratory evidence of infection, and a final diagnosis of cerebrovascular incident was reached in one of these. Influenza infection was confirmed serologically in the following three cases.

Case A.—Male, aged 9 years: "Influenzal" illness for two days in September, 1957, followed by vomiting, convulsions, and delirium for one day. Admitted dehydrated with tracheitis, Babinski sign positive on left side only, reflexes brisk in upper limbs but knee-jerks absent. The cerebrospinal fluid was normal. Improved to full recovery. Type A influenza C.F. titre rose from <8 (day 4) to 64 (day 13).

Case B.—Female, aged 12 years: "Influenzal" illness for four days in October, 1957, followed by recovery for two days, then coma progressing to death on eighth day after first symptoms. Type A influenza C.F. titre was 32 on seventh day. No virus was recovered from brain or lung removed at necropsy, which showed the presence of pneumonia and cerebral oedema with congestion of cortex, midbrain, and pons, and stippling of white matter. Microscopical examination showed no evidence of encephalitis.

Case C.—Female aged 18 years: "Influenzal" illness for one week in April, 1958, recovery for three days, then onset of restlessness and insomnia on ninth day. On admission, found to be hallucinated, inattentive, with slurring speech. Transferred from Ruchill to Stobhill Hospital as suspected schizophrenic, but improved and was dismissed well seven weeks after onset of symptoms. Investigations negative except for type A influenza C.F. titre 128 on both 14th and 24th days of illness.

Discussion

Our findings provide further evidence of the definite but small part played by adenoviruses in the causation of acute respiratory illnesses in the civilian population. In view of the recognized association between infection by certain adenoviruses and lymphoid hyperplasia, it is of interest that Case 2 indicates that these agents may also contribute to the "glandular fever" syndrome.

Since 1954 (Grist *et al.*, 1957) our tests have revealed altogether 19 cases of antigenic experience with an agent related to Sendai virus. The findings do not prove that these infections were caused by Sendai virus itself, particularly as this virus has been found to share antigens with mumps virus (Gardner, 1957; DeMeio and Walker, 1957), and with haemadsorption viruses of type 2 and perhaps type 1 (Chanock *et al.*, 1958). Since mumps virus also shares antigens with croup-associated virus (Chanock, 1956) and with type 1 haemadsorption virus (Chanock *et al.*, 1958), there is evidence of the existence of a group of myxoviruses with complex antigenic interrelationships. The various types of antibody response shown by our four cases tested with both mumps and Sendai antigens (Table III) may thus reflect the variety of antigenic composition of the infecting viruses, and perhaps also differing previous antigenic experience of such myxoviruses by the four patients.

The general features of the epidemic of Asian influenza in the Glasgow area resembled those reported from other parts of Britain. No antigenic variation of the virus was detected during the course of the outbreak, and the population was apparently immunized so adequately by the main autumn epidemic that only a minor resurgence of infection developed during the later months of winter, which are the usual time of seasonal prevalence of influenza in this area.

Our findings throw no new light on the relationship between influenza and encephalitis, but add another three to the cases in Britain recently reported by Dubowitz (1958), McGill and Goodbody (1958), Stephens and Cappell (1958), Morgan and Pickup (1958), and Dunbar *et al.* (1958).

Summary

Over 1,000 cases of acute respiratory illness were investigated virologically during two years. Ten cases of adenovirus infection were detected; one of these presented the features of glandular fever.

Ten cases developed complement-fixing antibodies to Sendai virus; of four such cases tested with mumps antigens, only two developed antibodies—one to both "V" and "S," one to "V" antigen alone. These findings suggest infection with a myxovirus related to but not necessarily identical with Sendai virus.

Type A influenza virus infections were detected during the autumn epidemic of 1957 and in the early months of 1958. No antigenic variation of the virus was detected. Three cases of encephalitis with serological evidence of influenza were encountered during the outbreak.

We are grateful to our numerous colleagues in hospital, general practice, and public health services for their co-operation; to Dr. A. Isaacs, of the National Institute for Medical Research, for supplying Asian prototype virus and for strain-identification of influenza viruses; to Dr. G. B. S. Roberts, University Lecturer in Pathology of Infectious Diseases, for necropsy findings in encephalitis Case B; to Dr. H. Gillies, of Stobhill Hospital, Glasgow, for clinical details of encephalitis Case C; and to Messrs. C. McLean, H. G. Carson, J. Kerr, and T. Roy for technical assistance during the study.

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ANAEMIA AND POLYCYTHAEMIA IN UNIOVULAR TWINS

BY

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The simultaneous occurrence of anaemia and polycythaemia in newborn monozygotic twins was first reported by Herlitz (1941–2), who described two such instances. Klingberg *et al.* (1955) and Bergstedt (1957) have reported similar cases, but none has so far been reported in Great Britain. In the past three years the syndrome has been recognized on four occasions in the Glasgow Royal Maternity and Women's Hospital. It seems worthy of comment, since in severe cases prompt treatment may be required. The findings in the cases previously reported are summarized in Table I, and in

TABLE I.—*Summary of Previously Reported Cases*

Author	Weight in g.	Sex	Hb	R.B.C. mil./c.mm.	Outcome
Herlitz (1941–2)	1,580	M	50%	1·94	Well at 6 years
	2,580	M	160%	7·02	" "
"	3,030	F	200%	6·86	" "
	2,220	F	65%	2·27	Died at 2 months. "Bronchitis"
Klingberg *et al.* (1955)	2,690	F	25·2 g./100 ml.	7·47	Uneventful
	1,770	F	3·7 "	1·85	"
Bergstedt (1957)	3,030	F	23·6 "	5·90	Well at 5 months
	1,810	F	13·6 "	3·90	" "

Table II the peripheral blood values in the present series are given. The following is a short history of the births and clinical findings in the four sets of twins.

Case 1

This patient, a 3-gravida, was delivered spontaneously of twin boys after 37 weeks' gestation. She was known to be rhesus-negative, but no antibodies had been detected. Apart from hydramnios, the pregnancy had been uneventful and the onset of labour was spontaneous.

The first twin, an assisted breech delivery, cried lustily at birth and weighed 2,570 g. The second child, a spontaneous vertex delivery, cried shortly after birth and weighed 2,680 g. This infant looked pale, the spleen tip was palpable, and the liver was enlarged to three fingerbreadths below the costal margin. Examination of the peripheral blood revealed a severe anaemia with a reticulocytosis, and many erythroblasts were to be seen in the film. Since the mother was known to be rhesus-negative, erythroblastosis foetalis was the presumptive diagnosis. The Coombs test on the cord blood was, however, persistently negative. Despite this finding, an exchange transfusion of 500 ml. was carried out.

The results of the examination of the cord blood of the first twin showed that he also had a negative Coombs test but that the haemoglobin level was remarkably high. Full blood examination confirmed the polycythaemia, but there was no excess of reticulocytes and the blood film was normal. Venesection was considered, but thought to be unnecessary.

The single placenta, which had been retained *in utero* and was therefore not available for inspection when the anaemia was discovered, was quite striking in appearance, in that one half was grossly congested with tortuous vessels, while the other half was pale with collapsed vessels.

Both babies made good progress. The plethoric infant had congested hands and feet for several days, and even on the eleventh day of life the haemoglobin remained very high at 20.5 g. per 100 ml.

Case 2

This patient, a nullipara, was well throughout her pregnancy, went into labour spontaneously after 34 weeks' gestation, and had normal vertex deliveries of twin girls. The first infant weighed 1,470 g. and on admission to the

TABLE II.—*Peripheral Blood Values in the Present Series*

Case No.	Weight in g.	Peripheral Blood				
		Sex	Hb (g./100 ml.)	R.B.C. (mil./c.mm.)	Retics. (%)	Film
1	2,570	M	21·8	8·66	2·3	Occasional erythroblasts
	2,680	M	7·7	2·20	19·0	Very numerous erythroblasts
2	1,470	F	20·0	5·57	2·2	Occasional erythroblasts
	1,080	F	8·3	2·28	15·0	Numerous erythroblasts
3	3,230	F	19·2	4·61	3·5	No abnormality
	2,190	F	14·1	4·42	7·3	" "
4	2,410	F	14·7	4·25	—	—
	2,490	F	21·8	7·00	—	—

premature baby unit was intensely cyanosed and had generalized oedema. The spleen was not palpable, but the liver was enlarged to three fingerbreadths below the costal margin. It was noted that the infant was plethoric compared with its twin, and this was confirmed by examination of the peripheral blood (Table II). Although the baby's colour improved with oxygen, respirations were never well established. At 3 hours her condition deteriorated. Venesection of 30 ml. of blood did not produce any improvement, and she died four hours after delivery. At necropsy there was congestion of all organs, the brain showing the presence of numerous small haemorrhages in the subependymal region.

The second twin weighed only 1,080 g. and cried shortly after birth. She was strikingly pale compared with her sister, and examination of the peripheral blood confirmed the anaemia. The Coombs test was negative.

Four and a half hours after delivery a transfusion of 40 ml. of blood was given into the umbilical vein. Her condition was satisfactory, considering the weight, until she was 13 hours old. Thereafter she had frequent apnoeic attacks and died at 18 hours. At necropsy there was some congestion of cerebral vessels, haemorrhage in the left adrenal gland, and widespread hyaline membrane formation in the lungs.

The placenta in this case was similar to that of the first, one side being grossly congested while the vessels of the other half were collapsed.

Case 3

This patient, a 4-gravida, was well throughout her pregnancy and went into labour spontaneously at term. The first twin was a spontaneous vertex delivery and cried at birth. She weighed 3,230 g. and was admitted to the well-baby nursery. At the age of 12 hours she was transferred

to the paediatric unit because she had become chilled and had developed generalized cyanosis. She improved quickly with the administration of oxygen, but the extremities remained cyanosed. Next morning it was appreciated that she was plethoric compared with her twin, and this was confirmed by examination of the peripheral blood (Table II).

The second twin weighed 2,190 g. at birth. She was an assisted breech delivery and was lethargic, but she improved quickly on admission to the premature-baby unit. On the second day examination of the peripheral blood revealed a mild degree of anaemia, for which no treatment was required. In neither twin were the departures from normal as severe as in the previous cases, and further progress was satisfactory. Unfortunately, by the time the condition was recognized the placenta was not available for inspection.

Case 4

This patient, a 6-gravida, was admitted to hospital at 35 weeks' gestation with a mild pre-eclamptic toxaemia. She went into labour spontaneously at 36 weeks and had two normal vertex deliveries.

The first twin weighed 2,410 g. and cried at birth. On the second day examination of the peripheral blood showed a mild anaemia, but no treatment was required.

The second twin weighed 2,490 g. at birth. At the age of 24 hours it was noted that her hands and feet were cyanosed, and examination of the blood showed a considerable polycythaemia.

Both infants were discharged home well. Regrettably, the placenta from this case had also been destroyed.

Discussion

In Case 1 the clinical picture was confused by the fact that the mother was known to be rhesus-negative. The infant was obviously in urgent need of blood, and, in spite of the negative Coombs test, the likeliest diagnosis at that early stage seemed to be haemolytic disease of the newborn: hence an exchange transfusion was done. In retrospect, a simple blood transfusion would have been just as effective as the exchange, but it is worth while noting that in the case described by Klingberg *et al.* (1955) an exchange transfusion was also given. Chown (1954) also carried out an exchange transfusion on an infant in whom the severe degree of anaemia at birth was later proved to have been due to bleeding of the foetus into the mother's circulation.

Observation of the first Glasgow case made it possible for the second to be readily recognized, and simple transfusion seemed the appropriate treatment. Venesection did not improve the plethoric twin, but both these infants were handicapped by their low birth weight. In the other two cases seen since no treatment was required.

It can be assumed that in all the cases described there must have been some direct communication between the circulations of the twins. Bergstedt (1957) confirmed this in his case by the injection of milk into one of the cords, with the result that both halves of the placenta became filled with milk. Klingberg and his co-workers also demonstrated arteriovenous shunts between the two placental circulations by perfusion of an artery in each cord with contrasting coloured fluids. The placenta in their case showed one half to be moderately red, without engorged vessels, and this they suggested supplied blood to the polycythaemic twin. The other half of the placenta was smaller and purple-red in colour with markedly distended veins; this half supplied blood to the anaemic twin.

That arteriovenous shunts occur in the placenta in uniovular twin pregnancies has been known for many years. Potter (1952) states that it is "common"; Browne and McClure Browne (1955) maintain that there is always a communication, and refer to the work of Schatz (1884) on the subject; Schatz believed that the anastomoses may be superficial or deep, and that, while the superficial ones may be either arterial or venous, the deep ones are always arteriovenous. These anastomoses are of significance because their presence in uniovular twins may explain why the death of one foetus is more common in uniovular than in binovular twins.

However, as anaemic and polycythaemic twins occur but rarely, some other factor must be present to produce the condition. One must postulate some obstruction to the return of the blood to the placenta from the plethoric infant, or obstruction of entry of blood in the anaemic one. This would agree with the placental findings—the engorged placenta of the anaemic twin and the absence of engorgement in the placenta of the polycythaemic one.

The nature of this obstruction is not easy to determine. In six of the eight cases summarized in Tables I and II the polycythaemic twin was the first to be born. Blood loss at the time of delivery is not recorded and is unlikely to be a factor. Pressure on one or other cord, or on a superficial vessel in the placenta, would produce such a condition, but proof is lacking, and, in any event, would be difficult to find. It would seem that the condition probably exists for some hours at least *in utero*, because of the presence of the reticulocytosis in the anaemic twin (Table II). More detailed study of the placentas might provide further information.

The syndrome, especially in a mild form, is probably more common than is realized, and the recognition of the severe case is important because treatment by transfusion may be urgently required. Neligan and Russell (1954), discussing foetal anaemia due to blood loss after incision of the placenta during caesarean section, maintain that the exsanguinated baby may appear deceptively well until shortly before death. They suggest that a transfusion is required if the peripheral blood haemoglobin level falls below 13.3 g. per 100 ml. in the first 24 hours of life. Presumably this level may be taken as a guide in all cases of acute anaemia in the newborn, whatever the cause.

Summary

Four cases of monozygotic twin pregnancy are described, in each of which one twin exhibited a polycythaemia and the other an anaemia.

In two of the four cases the anaemia was severe enough to warrant blood transfusion.

The aetiology of the syndrome remains obscure, but must depend on direct communication of the two foetal circulations.

My thanks are due to Professor Stanley Graham and Dr. J. H. Hutchison for their help in the preparation of this paper.

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INCIDENCE OF "MUSCLE PAIN" AFTER SHORT-ACTING RELAXANTS

A COMPARISON BETWEEN SUXAMETHONIUM CHLORIDE AND SUXAMETHONIUM BROMIDE

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Muscular pain and stiffness following the administration of short-acting relaxant drugs such as suxamethonium chloride, which act by depolarizing muscle fibres, was first reported by Bourne *et al.* (1952). Further reports of the syndrome were published by Currie (1953), Sanger (1953), Wordsworth (1953), Churchill-Davidson (1954), Price (1944), Hegarty (1956), Morris and Dunn (1957), and Prince-White (1957). Though slightly varying estimates were given of the frequency with which the phenomenon occurred, all authors agreed that the condition could temporarily be quite disabling and was not something to be dismissed lightly.

It is known from experiments on human volunteers that the muscular twitchings that precede the onset of paralysis when suxamethonium compounds are given are themselves painful, but the relationship of degree of fasciculation to post-operative pain is still not certain. There does not appear to be a direct relationship, but diminishing the fascicular movements by previously giving one of the curariform drugs or the slow administration of a dilute suxamethonium solution, on the other hand, does lessen the incidence of pain. It has also been established that the syndrome is rarely seen in patients who are confined to bed for some days after their operation. It is most pronounced in those who are ambulant at any early post-operative stage. The general picture that has emerged is similar to that seen in a man of sedentary habits who takes violent exercise, such as a game of squash or tennis; and then, 12 to 24 hours later, finds himself hardly able to move because of the pain and stiffness in his muscles.

Under tropical conditions of heat it is known that the ready-made solution of suxamethonium chloride undergoes decomposition and loses its potency (Keating, 1956; Lewis, 1956; Lomaz, 1956; Rajagopalan, 1956; Rollison, 1958). Bullough (1957) also describes this as having occurred in ampoules of suxamethonium chloride stored in warm surroundings in this country. A detailed investigation of the decomposition of suxamethonium chloride solutions has been made by Earles *et al.* (1954). They state that at room temperatures there is a 4.9% loss of potency in 12 weeks and 19.5% in one year. The risk of decomposition is eliminated by using suxamethonium bromide ("brevedil M"), which is dispensed as a powder to be dissolved just prior to administration. The present investigation was undertaken to determine whether there was any difference in the incidence of post-operative muscle pain if suxamethonium bromide was employed in place of suxamethonium chloride. That such a difference exists has been claimed by Ruddell (1957). It was thought that there might be some variation, for either of two reasons: (1) owing to the substitution of bromide for chloride as the cation radicle; or (2) owing to the differing methods of marketing of the two substances, with the consequent risk of decomposition in the case of the chloride.

Method and Material

We investigated 250 unselected patients admitted to hospital for oral surgery. The operations performed were removal of impacted wisdom teeth, multiple extractions, removal of dental cysts and unerupted teeth, and apicectomies. The patients were all clinically fit and their ages ranged from early adolescence to the middle fifties, the majority being between 20 and 45 years of age. There were 121 males and 129 females.

All the patients were premedicated with either "omnopon" and scopolamine or morphine and atropine in appropriate doses. The anaesthetic technique was as follows: induction with thiopentone and a short-acting relaxant, followed by endotracheal intubation (most commonly nasal) and insertion of a pharyngeal pack. Anaesthesia was continued with nitrous oxide and oxygen, supplemented when necessary with trichlorethylene or further doses of thiopentone. Post-operatively all patients were ambulant in the ward within 12 to 24 hours, and the majority were discharged from hospital on the day after operation.

So far as was possible, the anaesthetic routine described was used in every case, except that half the patients were given suxamethonium chloride as the short-acting relaxant and the other half received suxamethonium bromide. Dosages used were suxamethonium chloride 50–70 mg. and suxamethonium bromide 60 mg. The records of which drug was given to each patient were kept by the anaesthetist (R. A. L. L.), and the investigation and recording of the incidence of muscle pain and stiffness were made by the dental surgeons (D. S. H.-W. and R. A. J. M.). The latter questioned and examined all patients on the day after operation, before discharge from hospital, and seven to ten days later when they attended as out-patients. The dental surgeons had no knowledge of which relaxant drug had been employed in any patient. All doses of suxamethonium bromide were made up in 2 ml. of sterile normal saline, and the longest period between the making of the solution and its administration was two hours.

Results

There was, in fact, a striking similarity in the incidence of muscle pain and stiffness in the two groups: 46 (36.8%) patients who received suxamethonium chloride were affected and 45 (36%) of those who had suxamethonium bromide. The pain was similar in distribution and character to that previously described. It was commonest in the muscles of the chest, abdomen, and shoulder girdle, and in some cases was also present in the muscles of the limbs and neck. Again we confirm reports by other authors that the intensity of the muscular twitching occurring just before the onset of paralysis appeared to have no significant bearing on the

incidence of pain nor did the age of the patient, the muscular build, or the duration and precise nature of the operation performed.

There was, however, a remarkable sex variation. In both groups the incidence of pain and stiffness in females was almost exactly double that in males; the precise figures were:

Suxamethonium chloride ..	16 males	30 females
Suxamethonium bromide ..	14 „	31 „

This variation was mentioned by Currie (1953) and Hegarty (1956), but not by other authors. Two factors that may possibly have a bearing on this seem worth considering. First, assuming the analogy given in the last sentence of the second paragraph to be accurate, women, particularly married women between the ages of 20 and 40, tend to take less strenuous physical exercise than men, and on this ground one might expect an increased incidence. Secondly, a woman, particularly a married one with a young family, will in all probability have to take some exercise, in the shape of housework and other domestic duties, soon after discharge from hospital. She is thus likely to be exercising her muscles sufficiently to cause her to notice her symptoms. She is not in such a convenient situation as her husband, who can easily take a few days off work after his stay in hospital.

It is also of interest that few patients in each group (in fact, only seven in each) complained of pain in the first 24 hours. That the pain occurred only after leaving hospital does, in some measure, suggest that early ambulation plays an important part in its production.

Discussion

While there is no exact knowledge of the precise mechanism of production of this syndrome, we would fully agree with other authors that it does represent a not inconsiderable drawback to the use of depolarizing relaxant drugs in patients such as those who formed the material for this investigation, where early ambulation and discharge from hospital is the accepted practice. The clinical descriptions given by many of our patients follow very closely those recorded by Morris and Dunn (1957). On a few occasions patients have called in their general practitioner on account of the severity of the pain, especially when it has affected the chest and upper abdomen. In these situations it has often assumed a pleuritic character, leading to a diagnosis of pleurisy or even pneumonia. Some patients did, in fact, receive a course of antibiotic therapy on these grounds. Price (1954) states that in his experience the pain in the neck and back muscles has been so severe that a diagnosis of poliomyelitis or meningitis has provisionally been considered.

Some method of prophylaxis is to be desired. The most successful is alleged to be that advocated by Morris and Dunn (1957). They advocate the giving of small doses of gallamine triethiodide or D-tubocurarine chloride two to three minutes prior to the induction of anaesthesia with thiopentone and the short-acting relaxant. Using gallamine triethiodide, they give 40 mg. and with D-tubocurarine chloride 5 mg. This has the effect of diminishing the response of the muscle fibre to the depolarizing drug as regards the intensity of the muscular twitchings. They state that the incidence of pain and stiffness is thereby reduced to around 5%. The use of two relaxant drugs which act through different pharmacological mechanisms simultaneously is, however, open to objection. As Hodges (1957) has pointed out, any variation from the expected response of the patient to either drug will produce a situation which will, at least, be inconvenient to the anaesthetist and, at worst, may be one of extreme danger to the patient. In addition the use of gallamine and D-tubocurarine does not completely abolish the post-operative pain. Further work is necessary if a most convenient and useful anaesthetic technique is to be made free from undesirable side-effects from the patient's point of view.

Summary and Conclusions

Suxamethonium bromide was used as the relaxant for endotracheal intubation in 125 patients undergoing oral surgery, and the incidence of post-operative muscle pain was compared with a parallel series in which suxamethonium chloride was used. No significant difference in the incidence was noted.

In both series women showed a greater incidence than men, and a suggested reason for this fact is given.

Agreement is expressed with the views of other authors that the likelihood of post-operative pain represents a serious disadvantage to the use of short-acting relaxants in patients where early ambulation is desired.

We would like to acknowledge with gratitude the kind and helpful collaboration of May and Baker Ltd., who also supplied the brevedil M with which this trial was carried out.

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Six students from the Westminster Medical School have recently returned from a scientific expedition to the Belgian Congo. The work they did included a general medical survey of the village of Yalolia on the North bank of the Congo River. There were 203 members of the forest-dwelling Turumbu tribe in the village, and a representative quarter—51 men, women, and children—were examined. The incidence of various pathological conditions in this sample was filariasis (*perstans*) 37 (74%), ankylostomiasis 25 (50%), tinea skin infections 17 (34%), onchocerciasis 11 (22%), scabies 9 (18%), *Enterobius vermicularis* infection 8 (16%), yaws 7 (14%), M.T. malaria (proved by blood examinations) 5 (10%), tropical ulcers 4 (8%), leprosy 2 (4%), eosinophilia 44 (88%), hepatomegaly 32 (64%), splenomegaly 23 (46%), monocytosis 7 (14%), anaemia 40 (80%).

Medical Memoranda

Sphygmomanometer Cuff Calibrated for Corrected Blood-pressure Readings

Many practitioners who are constantly engaged in taking blood-pressure readings must from time to time have been puzzled by very high or very low readings in patients who are perfectly normal in health and symptom-free. There are, of course, many factors which can affect B.P. readings in people in normal health. These have been fully described by Professor Pickering (1955). One source of error which he describes, and which allows of immediate correction in reading the B.P., is the effect of differences in the arm circumference.

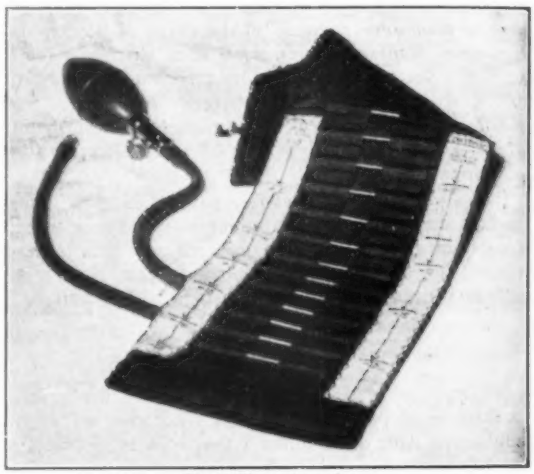
This phenomenon was originally described by Ragan and Bordley (1941), who compared a series of direct auscultatory B.P. readings in one arm with simultaneous ones recorded by arterial puncture and a Hamilton manometer in the other. Pickering *et al.* (1954) applied these findings to a population sample, deducing two formulae by which the systolic and diastolic variations could be expressed from the tables of Ragan and Bordley, and confirmed that their validity was unaffected by age, height, or other factors.

While being interested in eliminating this source of error, I found it to be somewhat tedious and time-consuming to have to measure each arm with a tape measure and then to refer to a table in order to arrive at the correct result in each case. Having recently acquired the new hook-type armlet made by Accoson, I thought that this difficulty could be overcome by calibrating the armlet for these corrections. The finished job, which is shown in the illustration, serves the purpose most effectively and is used constantly by me. The correct additions or subtractions for systolic and diastolic readings can be read off instantaneously.

The actual calibration of the cuff is not, however, a very simple matter. This hook-type armlet has a series of 13 steel ribs sewn transversely into the material of the cuff, and the other end of the cuff is clipped or hooked into these ribs with one of two hooks, one of which lies 0.5 cm. behind the other, thus giving a total of 26 different positions for the various arm circumferences. Mathematically there is a difficulty here in that the spacing of these ribs does not allow of a simple arithmetical progression of circumference, because, as the arm circumference gets smaller, the amount of material of the cuff which is folded underneath is greater; and this alters the differential between the external and internal circumference of the cuff when in position on the arm.

In order to equate arm circumference with the internal circumference of the cuff for the different positions of the hooks, I found it was necessary to hook the end of the armlet on to each rib with each of the hooks in turn, fold it flat, and measure the internal length with a straight ruler; clearly, this measurement doubled gives the internal circumference. After these measurements had been tabulated, it was found that they showed an irregularity in sequence, and that the best way to get an approximately accurate calibration for each position was to plot the readings on a piece of graph paper and draw a straight line between the two end ones, when, by a stroke of good fortune, I found this line to run, more or less, through whole numbers and multiples of five centimetres. Once these measurements were obtained, it was then a simple matter to calibrate the arm band, not in centimetres, etc., but in the actual subtractions and additions laid down in Ragan and Bordley's tables. The calibrations were marked in indian ink on two strips of white tape sewn on to the cuff on both sides of the ribs, one side for diastolic corrections, the other for the systolic ones. When the appropriate hook is engaged with its rib, the figures left uncovered by, and just beyond, the overlying edge of the hooked end of the cuff indicate the corrections for this arm circumference.

Although the above method of calibration has been a convenient and quick means of translating measurements of arm circumference into armlet calibrations it is pointed out by Dr. G. S. C. Sowry (1958, personal communication) that the most accurate way would be to carry it out on a series of living human arms under standard conditions—for example, tension of measuring tape. He also states that the error introduced by arm circumference is small compared with the time-to-time variation in any individual, that its main use would be in interpretation of data from groups, but that it might be of value for those doing insurance examinations.



The calibrated armlet.

It is felt, however, that armlets could be manufactured with these calibrations already inserted, so that the correction may be seen at a glance. Whether or not they should be applied in individual cases would be for each observer to decide for himself; their availability should add clinical interest.

For my own part I have been surprised, having used this cuff regularly for the last twelve months, how otherwise puzzling readings become much more explicable. As these tables are not yet in common use I make a note in my records of the fact that the readings are corrected, because there is often a considerable variation from the straight readings.

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Reviews

DOCTOR TO LIEUTENANT-GOVERNOR

Varied Operations. An Autobiography. By the Hon. Herbert A. Bruce, M.D., F.A.C.S., L.R.C.P., F.R.C.S.(Eng.). (Pp. 366+xiv; illustrated. $6.) Toronto: Longmans, Green and Co. 1958.

This charming autobiography was published on the ninetieth birthday of its author and draws a vivid picture of the days that are gone. Beginning the study of medicine 70 years ago in the unorganized medical school of Toronto, he has witnessed and helped more than any other its progress to this day, when it has one of the finest universities and medical schools in the world. The book breathes his love for this, our country, its Royal Family, and its institutions; not forgetting the Royal College of Surgeons, where he passed the Fellowship examinations in 1896, being examined by Sir Rickman Godlee and receiving his Fellowship at the hands of Sir William MacCormac. The account of his days at University College Hospital, his general practice in London, and his life as a ship's doctor draws a fascinating picture of the past. For instance, in 1895 he attended a "coming-out" luncheon for Dr. Jameson after he had served his six months in prison for organizing his famous raid in Johannesburg.

Dr. Bruce has a fiery and attractive personality, stemming from his Irish origin (Enniskillen in County Fermanagh), and in his life he stepped gaily from one controversy to the next, with never a dull moment. Outstanding among these was the almost unbelievable story of his joining the Canadian Army Medical Corps in 1915. In the hospital at Le Tréport, not being allotted surgical duties, he absconded, bluffed his way on to the leave boat at Boulogne, repeated this at Liverpool, and back to Canada, arriving there before his C.O. knew he had left. He was then made Inspector-General of the Canadian Medical Services, and went back to France, one conjectures, inspecting the hospital from which he had departed so brusquely, with his former C.O. standing stiffly to the salute with hyperaemic facies. He then published a stinging report on the Canadian Army Medical Corps and joined our R.A.M.C. Later in the same war he went on a good-will tour of the United States with Sir Arbuthnot Lane and Sir James Mackenzie. He ended his surgical career when he became Lieutenant-Governor of Ontario for six successful years. After this, at 72, he entered the Parliaments at Toronto and Ottawa and there pursued his quixotic course, including the high point of suspension from the House.

The book bristles with humour, such as the story of the deaf obstetrician who, being asked if it was a boy or a girl, replied, "I don't mind if I do"; or the presentation of a bustled dress to Queen Victoria which played "God Save the Queen" when the wearer sat down. She apparently was not amused on *a priori* or *a posteriori* grounds. The delightful foreword by the present Premier of Canada, John Diefenbaker, epitomizes Bruce's life in the words of Dr. Johnson: "He lived more hours in the broad sunshine of life than any man." After reading this book one feels great gratitude to the author for undertaking this task at his age, and letting us join him in his Odyssey down the years from 1868 to 1958.

A. DICKSON WRIGHT.

LEPTOSPIROSIS

Leptospirosis in Man and Animals. By J. M. Alston, M.D., F.R.C.P.Ed., and J. C. Broom, O.B.E., M.D. With a chapter on Legal Responsibility by C. J. A. Doughty, B.A. (Pp. 367 +xii; illustrated. 40s.) Edinburgh and London: E. and S. Livingstone Ltd. 1958.

Only two varieties of *Leptospira* exist in Great Britain, and human infection is rare. Unless contracted by bathing in rat-infested rivers or by contact with an infected dog, the disease is occupational, affecting workers in sewers, fish docks, and mines, and on farms where pigs are infected. It has been discovered only within the past 25 years that many other serotypes of *Leptospira* occur in other countries; and where, as in rice-growing areas or sugar-cane plantations infested with rats and other rodents, large numbers of agricultural workers are exposed to infection, leptospirosis is much more common, although the disease so caused is generally less severe. The rational study of this disease therefore has a relatively short history, and the full account of it provided in this book fills what now seems an obvious gap in the literature.

Every aspect of the subject is dealt with: its history from Weil's description of the disease whose cause was to be discovered in Japan nearly 30 years later; the character of the micro-organism; modes of infection; the clinical features, morbid anatomy, and diagnosis of different forms of the disease in man; epidemiology and regional distribution; and the disease in animals. The authors emphasize that in Weil's disease as we see it involvement of the kidney is more important than that of the liver, and that the level of the blood urea is the surest guide to prognosis; it might perhaps be more strongly emphasized that albuminuria and leucocytosis distinguish leptospirosis from epidemic hepatitis, since awareness of this can save unnecessary laboratory work in patients with the latter disease. Conclusions on therapy are pessimistic: the value of immune serum is not adequately proved, and there is no good evidence of benefit from penicillin or other antibiotics given at the time when a diagnosis is usually made. No attempt is made to reconcile this finding with the high susceptibility of the organisms to antibiotics *in vitro*—a discrepancy for which there must be some explanation.

The book abounds in interesting and little-known facts, such as the altered seasonal incidence of leptospirosis in Holland during the war caused by people falling into canals in the black-out. There are full-page illustrations of Weil, Inada, Noguchi, and Schüffner, and of various environments in which leptospirosis can be acquired, including a picturesque canal scene in Amsterdam and an English river (unnamed) with three bathers in it. This appears broad, sylvan, and inviting, and might thus drive any would-be bather solicitous for his own health straight into the sea. It is perhaps too much to ask for a black-list of British waters known to have been polluted.

L. P. GARROD.

ORGANIZATION FOR SURGERY

Praktische Operationskunde und Instrumentenlehre. Leitfaden für das Operationspersonal. By Harro Seyfarth and Elly Jaeger. (Pp. 448+xvi; illustrated. DM. 36.70.) Jena: Gustav Fischer Verlag. 1958.

The performance of an operation and the care of the instruments used involves a large staff of highly trained technicians without whose assistance no surgeon could

possibly carry out his work. This admirable manual supplies with precision and clarity all the information which they require, and the fact that it has been written by a surgeon in active practice and his own theatre sister is sufficient evidence that it is just what is needed for the formation of a well-organized team. Beautifully illustrated and really well arranged, it is a model of what such a manual should be, and it will repay the careful study of any who are called on to organize the service of a theatre. The young surgeon will find here a mine of information, and there are few pages from which even the most experienced may not gather useful hints. The great capacity of the German mind for organization is shown at its best.

In defence of our own country we would make two points. The eyeless needle, which was first made at the London Hospital in 1922, seems to have only just reached Germany, and there is no hint of the superb technical perfection it has now achieved. And only a limited account is given of the modern apparatus for general anaesthesia—but one has to remember that until quite recently all general anaesthesia was given by the nurses, because, as a well-known surgeon once said, they understand it.

HENRY SOUTTAR.

GANGWAY FOR DOCTORS

The Phantom Limb. By Hamilton Johnston. (Pp. 254. 15s.) London: Victor Gollancz. 1958.
Gangway for the Lady Surgeon. By Wynne O'Mara and Eleanor Buckles. (Pp. 176. 12s. 6d.) London: Robert Hale, Ltd. 1958.

Doctors and detectives can knock on any door, which probably accounts for the popularity of both these unwelcome visitors as novelists' puppets. Most of the books about doctors which pour from publishers' warehouses have as little connexion with medicine as Trollope's books about clergymen had with piety, and expecting to find lifelike practitioners in them is as unreasonable as expecting the *Army List* to resemble *The Army Game*. But Dr. Johnston's publishers insist that *The Phantom Limb* is a novel "above all remarkable for its quality of remorseless truth" on life in the N.H.S. Discovering exactly what goes on in another man's practice is as difficult as discovering exactly what goes on in another man's house, but I doubt if all 47-year-old G.P.s have querulously neurotic wives for both themselves and their assistants, get into bed with their lady-novelist patients during the afternoons, and in teashops plot irregular week-ends with other doctors' wives. Contemporary tales of medical practice, like contemporary tales of imprisonment, seem to be either dramatic or gay, but Dr. Johnston makes it all rather furtive.

There is nothing furtive about *Gangway for the Lady Surgeon*, Dr. O'Mara's bright little romp on the ocean. Books about doctors at sea have suffered from catatonic rigidity since the best of them all, J. Johnston Abraham's *Surgeon's Log*, was published in 1911. There is always the crew's embarrassing distrust of their medical adviser, the horrifying fate of former doctors and the horrifying seasickness of the current one, muddling the medicines in the ship's dispensary, rows with the captain, and the alarming operation afloat. Dr. O'Mara gets the lot, plus the complication of her shipmates picking her a suitable husband *en route*.

RICHARD GORDON.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Chirurgie der Arterien. By Dr. K. Kremer. (Pp. 280+viii, illustrated. DM. 59.) Stuttgart: Georg Thieme Verlag. 1959

Praktische Hämatologie. Differential-diagnose, Therapie Methodik. By Prof. Dr. H. Begemann and Dr. H.-G. Harwerth. (Pp. 264+xi; illustrated. DM. 29.80.) Stuttgart: Georg Thieme Verlag. 1959.

Cardiovascular Sound in Health and Disease. Being a Comprehensive Treatise, introduced by a Historical Survey. By Victor A. McKusick, M.D. (Pp. 570+xii; illustrated. £6.) London: Baillière, Tindall and Cox. 1958.

Physiologie und Experimentelle Pathologie der Leber. By Dr. Anton Fischer. (Pp. 187; illustrated. 46s.) Budapest: Akadémiai Kiadó. Berlin: Akademie-Verlag. 1959.

Blastogenese des Menschen. By Karel Mazanec, M.D. (Pp. 179; illustrated. DM. 20.60.) Jena: VEB Gustav Fischer Verlag. 1959.

A Doctor's Story. By Sir Fred Bowerbank. (Pp. 341; illustrated. 30s.) Wellington, N.Z.: Harry H. Tombs Limited. 1958.

The Pneumoconiosis Problem. With Emphasis on the Role of the Radiologist. By Eugene P. Pendergrass, M.D. (Pp. 146+x; illustrated. 51s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

The Demonstration Clinic for the Psychological Study and Treatment of Mother and Child in Medical Practice. By David M. Levy, M.D. With a preface by Leona Baumgartner, M.D. (Pp. 120+xxviii. 37s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The Roots of Psychoanalysis and Psychotherapy. A Search for Principles of General Psychotherapeutics. By S. A. Szurek, M.D. (Pp. 134+viii. 32s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Basic Issues in Psychiatry. By Paul V. Lemkau, M.D. (Pp. 106+vii. 25s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Clinical Flame Photometry. By Henry A. Teloh, M.D. (Pp. 103+xvi. 34s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Physical Diagnosis. The History and Examination of the Patient. By John A. Prior, M.D., Jack S. Silberstein, M.D., and contributors. (Pp. 388; illustrated. 56s.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

Obstetric and Gynecologic Milestones. Essays in Eponymy. By Harold Speert, M.D. (Pp. 700+ix; illustrated. £5 5s.) New York, London: Macmillan Company. 1958.

Dorsalgias Interescapulares. By V. Bosch Olives. (Pp. 157; illustrated. 50 pesetas.) Barcelona: Administración Queromón Editores, S.A. 1958.

La Disproteinemia Nefrósica. Estudio Clínico y de Laboratorio. By Andrés Olivé Badosa. (Pp. 136. 50 pesetas.) Barcelona: Administración Queromón Editores, S.A. 1958.

A History of Ophthalmology. By George E. Arrington, Jr., M.D. (Pp. 174+xvii. $4.) New York: MD Publications, Inc. 1959.

The Eternal Search. The Story of Man and His Drugs. By Richard R. Mathison. (Pp. 308. 21s.) London: Frederick Muller Limited. 1959.

The Enzymes. Edited by Paul D. Boyer, Henry Lardy, and Karl Myrbäck. Second edition. Vol. I. Kinetics, Thermodynamics, Mechanism, Basic Properties. (Pp. 785+xi; illustrated. $24.) New York: Academic Press Inc. 1959.

Pathophysiology in Surgery. By James D. Hardy, M.S.(Chem.), M.D., F.A.C.S. (Pp. 704+xx; illustrated. £7 12s.) London: Baillière, Tindall and Cox, Ltd. 1958.

Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. By Howard W. Jones, Jr., M.D., and William Wallace Scott, M.D., Ph.D. (Pp. 456+xvi; illustrated. £6 8s.) London: Baillière, Tindall and Cox, Ltd. 1958.

Das Akute Abdomen im Kindesalter auf Grund angeborener Anomalien. By Václav Tošovsky, M.D., and Otto Vychytil, M.D. (Pp. 159; illustrated. DM. 24.70.) Berlin: VEB Verlag Volk und Gesundheit. 1958.

BRITISH MEDICAL JOURNAL
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NEW HOSPITALS FOR OLD

Impressive new buildings for commerce and industry are springing up all over the country, but of new hospital buildings there is virtually nothing to be seen. The inadequacy of many existing hospitals is plain to all, and it was the urgency of the need for rebuilding which prompted the B.M.A.'s Central Consultants and Specialists Committee to appoint two of its members, Mr. A. Lawrence Abel and Mr. Walpole Lewin, to investigate the present position. Their report to the Committee is the first of five contributions on hospital building and planning which we publish in this week's *Supplement*.

Abel and Lewin ask for a substantial increase in the capital allocation for the hospital service, and no one who has any knowledge of British hospitals can doubt that this is a reasonable demand. Two-thirds of the hospitals are nearly 70 years old, and one-fifth are approaching their century. In 1945 a thorough survey of the hospitals was carried out, and the inspectors of that time condemned much that they saw. The £10m. per annum which was the average capital allocation for the whole of the hospital service for the first eight years of the N.H.S. did little more than slightly ease the congestion caused by the enormous demands for treatment. Yet at the same time Great Britain can justifiably claim to be in the forefront of medical progress. Therapeutic advances continue to be made in buildings which by any standard are outmoded and outdated. More patients, too, are being treated in them: in 1957 nearly 30% more patients were discharged from hospital after treatment than in 1949, though during the same period there was an increase of only 6% in occupied beds.

In the country as a whole in 1952–3 the capital sum spent on hospital buildings was 4.1% of the hospital running costs, rising to 5.4% in 1956–7, and this after the years of neglect during the war. Before the war the capital expenditure was a much higher percentage of the running costs, from 20 to 30%. The Guillebaud Committee recommended an expenditure of £30m. a year in terms of 1955 costs at a time when £11m. per annum was being spent on hospital building. Abel and Lewin suggest an expenditure of £75m. per annum for ten years, and add that this would probably result in a substantial lowering of running costs—a contention supported by the evidence put before the Guillebaud Committee. According to the Civil Estimates published last week the Government will spend £22,250,000 on hospital building in England and Wales this year. This is only £2m. more than last year.

With the advent of the N.H.S. some of the hospital authorities were slow off the mark, and the administrative machinery, divided between the regional hospital boards and the Ministry of Health, was not always smooth-running. Indeed, the Select Committee's report[1] on Treasury control was critical of both the Ministry and the Treasury, and suggested that the role of the partners was inverted, the Treasury "exercising little control where they have a right to make their influence felt" but "exercising a fairly tight control in a field where the Department (Ministry) might expect to be left with more responsibility." These are administrative defects which are capable of remedy, but structural deficiencies cannot be made good without money. The recent report[2] of the Nuffield Provincial Hospitals Trust on sterilizing practice in hospital revealed a deplorable state of affairs. Central sterilization, commonplace in America, is a rarity in British hospitals. Most operating theatres are without modern ventilation, and wards have no dressing-rooms or accommodation for isolating infected cases.

The present need is not so much for more hospital beds as for better hospitals in the right places. Many hospitals are so old that they should be abandoned and rebuilt only as part of a larger hospital centre, with modern diagnostic and treatment facilities and full medical and nursing staff at all levels. Professor T. McKeown's stimulating ideas (*Supplement*, p. 122) on hospital planning emphasize the relationship of the hospital to the community as a whole. It must be accessible and provide beds of special kinds now usually found only in separate hospitals. Only a quarter of the out-patients seen at hospitals receive treatment as in-patients, and much of the work of a hospital is done outside the wards. Dr. John Fry (*Supplement*, p. 124) sees the hospital as the leader of the local health services, but he is not in favour of a nation-wide scheme to give family doctors beds in hospitals. Here his views depart somewhat from those of Abel and Lewin, who agree with the B.M.A. that the smaller hospitals should be staffed by general practitioners.[3]

[1] Sixth Report from the Select Committee on Estimates, *Running Costs of Hospitals*, 1957. H.M.S.O., London.
[2] *Present Sterilizing Practice in Six Hospitals*, 1958, Nuffield Provincial Hospitals Trust. See leading article, *Brit. med. J.*, 1958, **2**, 1582.
[3] See *Brit. med. J. Supplement*, 1952, **2**, 49.

About the design of hospital buildings there is still much to be learned. The experimental wards to which Mr. L. Farrer-Brown refers (*Supplement*, p. 118) will in due course provide their lessons. Changes in medicine are taking place rapidly, and every clinician asks for flexibility in design. Abel and Lewin are no exception, asking as they do for a "shell ward or out-patient unit, it then being left to local planning to adjust it to their particular requirements." But they are wise in recommending clinicians to accept some basic designs in hospital construction and to avoid a tailor-made hospital to fit the individual whims of consultants. They mention the interesting proposal that all major hospitals should have a "fallow" ward. This could also be a convalescent ward to which patients who are up and about could go for four or five days before discharge. The few hospitals which have such wards regard them as invaluable, for they allow maximum occupancy without overcrowding of the active treatment wards.

Dr. G. E. Godber (*Supplement*, p. 115) makes a plea for the proper briefing of architects, who may solve the problems put to them in different ways, and for a realistic approach without "inessential architectural extravagance." This does not mean that hospital architecture should be reduced to a dull and uniform pattern; far from it. It is the architect's skill which will help the hospital service to get the best value for money. The important thing is that building and experimentation should go on, with the recognition that the hospital is a living entity, with changes occurring in its constituent elements at different rates. The risk of making mistakes must be run; and they can be profitable if the lessons learned from them are put to good use elsewhere. It is high time our hospitals became more efficient tools for the job they have to do in the National Health Service and began to compare favourably with those of other civilized countries.

HEART FAILURE AND HYPONATRAEMIA

The clinical picture of intractable heart failure is all too familiar. The patient's emaciated pinched face and wasted arms contrast with his shiny, oedematous legs and protuberant, ascitic abdomen. The pressure is raised in the jugular veins, which pulsate with each right ventricular systole. Functional tricuspid incompetence also increases the hepatic engorgement, and in time cardiac cirrhosis imparts the sallow tinge of mild hyperbilirubinaemia to the patient's skin. The response to diuretics is absent or poor, and any increase in urine excretion is usually associated with a greater loss of potassium than sodium. A ready liability to develop intolerance to digitalis adds to the patient's discomfort, and a marked reduction in glomerular filtration rate is reflected in a rise of blood urea. Clinicians are also familiar with the development in these patients of a low concentration of sodium in the serum, and have come to recognize this as an ominous prognostic sign. Despite its frequency and much experimental study, the mechanisms responsible for hyponatraemia in chronic cardiac failure are still far from clear.[1–10]

Overhydration with water, induced experimentally by giving antidiuretic hormone, or occurring clinically in anuria or after operations, lowers the serum sodium level in the presence of a normal total amount of sodium in the body. Sodium depletion due to renal losses in salt-losing nephritis or adrenal insufficiency may cause hyponatraemia associated with a decrease in the total body sodium. Less readily understood is the hyponatraemia found in many chronically ill patients, particularly those with intractable oedema from any cause, in the presence of a raised or normal total sodium content of the body. There is some evidence to suggest that metabolic disturbances (perhaps due to hypoxia) so damage the cells that intracellular osmolarity is reduced, with a consequent readjustment of the osmotic pressure in the extracellular fluid by a lowering of the sodium concentration[11]—a situation euphemistically called the "sick-cell syndrome."

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[4] —— Crosley, A. P., and Elkington, J. R., ibid., 1951, **4**, 868.
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[6] Friedberg, C. K., *Circulation*, 1957, **16**, 437.
[7] Danowski, T. S., Fergus, E. B., and Mateer, F. M., *Ann. intern. Med.*, 1955, **43**, 643.
[8] Levitt, M. F., *Arch. intern. Med.*, 1957, **100**, 364.
[9] Bayliss, R. I. S., in *Modern Trends in Endocrinology*, 1958, London, p. 130.
[10] Wynn, V., and Rob, C. G., *Lancet*, 1954, **1**, 587.
[11] Elkington, J. R., Winkler, A. W., and Danowski, T. S., *J. clin. Invest.*, 1948, **27**, 74.
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[15] Cattan, R., and Vesin, P., *Semaine Hôp. Paris*, 1956, **32**, 712.
[16] Dresdale, D. T., Greene, M. A., and Guzman, S. V., *Amer. Heart J.*, 1958, **55**, 851.
[17] Schreiber, S. S., Bauman, A., Yalow, R. S., and Berson, A. S., *J. clin. Invest.*, 1954, **33**, 578.
[18] Gunton, R. W., and Paul, W., ibid., 1955, **34**, 879.
[19] Farber, S. J., and Soberman, R. J., ibid., 1956, **35**, 779.
[20] Oleesky, S., and Stanbury, S. W., *Lancet*, 1951, **2**, 664.
[21] Lasche, E. M., and Durant, T. M., *Amer. J. med. Sci.*, 1957, **233**, 80.
[22] Berliner, R. W., and Davidson, D. G., *J. clin. Invest.*, 1956, **35**, 690.
[23] Raisz, L. G., McNeely, W. F., Saxon, L., and Rosenbaum, J. D., ibid., 1957, **36**, 767.
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[25] —— —— Chandler, D. E., and Myers, G. B., *Circulation*, 1955, **11**, 615.
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[27] Hills, A. G., Chalmers, T. M., Webster, G. D., and Rosenthal, O., ibid., 1953, **32**, 1236.
[28] Riddle, M., Gardner, F., Beswick, I., and Filshie, I., *Brit. med. J.*, 1958, **1**, 1274.
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Elsewhere in this issue Drs. J. N. Mickerson and J. Swale describe the diuretic effect of corticosteroid in patients with obstinate heart failure and hyponatraemia (p. 876). There is no question that some patients with intractable oedema benefit from steroid treatment, as others have shown before,[12-16] but there is difficulty in accepting, without further experimental support, the hypothesis of Mickerson and Swale that the hyponatraemia is due to adrenal insufficiency caused by anterior pituitary exhaustion, and that the beneficial effect of prednisolone is a consequence of adrenal substitution therapy. Buccal pigmentation is decidedly uncommon in secondary hypo-adrenalism, and the suggestion that increased pituitary activity earlier in the course of the disease, but later giving way to exhaustion, causes thyroid overactivity would be more convincing if supported by radioiodine studies or measurement of the protein-bound iodine level. Despite a reduction in total body sodium, adrenal insufficiency is not usually associated with marked hyponatraemia because of a concomitant loss of body water and a reduction in the extracellular fluid volume. In contrast, the total body sodium is increased in cardiac failure and the plasma volume is expanded.[17-19] In chronic adrenal insufficiency infusions of saline temporarily restore the extracellular fluid volume and improve the patient's condition, whereas in the hyponatraemia of cardiac failure intravenous saline usually induces intolerable thirst and increases the oedema. Furthermore, cortisone restores water diuresis to normal in the Addisonian or hypopituitary patient,[20] whereas it fails to do so in patients with severe cardiac failure.[21] Nor, because of changes in renal clearances, can much reliance be placed on the urinary excretion of 17-ketosteroids or "corticoids" as an index of adrenocortical function in such patients. The excretion of 17-ketosteroids is depressed in any serious illness, and in the presence of a low glomerular filtration rate the urinary excretion of 17-hydroxycorticosteroids may be low at a time when the plasma level is high.

Some workers[12 15] have suggested that the diuresis induced by steroid therapy is due to suppression of aldosterone secretion by pituitary inhibition, or to competition with aldosterone in the renal tubular cells. This is unlikely because adrenalectomy may not free the patient of oedema, and more specific aldosterone competitors, such as spirolactone, are not potent diuretics. It seems more probable that corticosteroids either improve renal function or favourably influence some ill-understood disturbance of cellular metabolism in general. It is now clear that the ability to excrete dilute urine, which would correct hyponatraemia due to water retention, disappears when the glomerular filtration rate is reduced and only a small solute load is presented to the tubules.[22] Corticosteroids may increase the glomerular filtration rate, but, more important, in normal subjects on a salt-poor diet, they increase maximum urine flow and free-water clearance by an action on the renal tubules which is independent of antidiuretic hormone activity.[23] As to cellular metabolism, some measure of the disturbance in cardiac failure is shown by the marked potassium depletion that occurs from loss of intracellular potassium,[24 25] an effect often aggravated by the long-continued use of diuretic agents. In patients with hyponatraemia small amounts of potassium may sometimes raise the concentration of sodium in the serum and promote a diuresis.[26] Equally corticosteroids influence the transport of potassium into, and sodium out of, the cells[27]; they increase the patient's appetite and often impart a sense of well-being.

Even though the cause of hyponatraemia in chronic cardiac failure remains unexplained, there is good evidence that the situation is often aggravated by overdosage with digitalis and the relentless administration of diuretics.[6 8] Diuretics should be used only when they produce a diuresis of sodium and water, and in maintenance therapy the smallest dose should be used as infrequently as possible to keep the patient free of oedema. On page 883 in this issue Drs. W. A. Leff and H. E. Nussbaum describe their results with chlormerodrin, an organic mercurial compound effective by mouth. About 10% of their cases developed gastro-intestinal disturbances, but the remainder were adequately controlled, and none developed evidence of renal damage. Fear of toxicity to mercurial diuretics has never been an important issue in Great Britain, although on rare occasions the development of nephrosis has been attributed to mercurial poisoning.[28 29]

HYPERTROPHIC PYLORIC STENOSIS IN THE ADULT

More than 100 years have passed since the adult form of hypertrophic pyloric stenosis was first described by Cruveilhier.[1] Though his patient was a woman, it is now known that men are affected about four times more often than women.[2]

Occasionally symptoms extend back to early childhood and indicate the presence of mild, chronic pyloric obstruction. More often a history varying widely in duration is obtained, suggesting either an atypical presentation of peptic ulcer, or pyloric stenosis

due to simple ulcer or gastric cancer, of which Drs. J. A. Balint and M. P. Spence describe a series of cases at p. 890 of the *Journal* this week. The typical radiological appearances[3] of hypertrophic stenosis in the adult show a lengthened, smooth, narrowed pyloric canal with a regular proximal end and a duodenal bulbar impression distally. These appearances only occasionally permit of a tentative diagnosis, and gastroscopy adds little of diagnostic value.[4] At operation the diagnosis will probably still be in doubt, and the possibility of a carcinoma is often difficult to exclude. For this reason a small distal gastrectomy is the treatment of choice, continuity being established by a Billroth I type of anastomosis. Rarely, the history, *x*-ray findings, and operative appearances will strongly suggest hypertrophic stenosis, and, provided an immediate histological examination can be done, a simple pyloroplasty will avoid resection of the stomach and is known to give excellent results.

Although the cause of hypertrophic pyloric stenosis is not known, the infantile and adult forms have a similar pathology, and there is reason to believe that the latter represents a less severe but persistent type of the infantile variety. In most children who have had a Ramstedt operation performed for congenital pyloric stenosis the tumour will be absent if looked for at any subsequent laparotomy. On the other hand, if surgical treatment in infancy was by gastro-enterostomy, the pyloric tumour may still be present.[5] Further, *x*-ray follow-up studies[6–8] in children and adults who have had the congenital type of disease (no matter how treated) show that about one-third of the subjects have persistent narrowing in the pyloric region.

The incidence of peptic ulcers associated with hypertrophic pyloric stenosis in adults is high[7 9]: 18 of 25 cases seen at a London hospital[10] and 50 of 81 cases at the Mayo Clinic[11] were found to have both conditions. The frequency of this association suggests that there may be some relationship between the two diseases. Output of acid from the stomach is known to increase with increasing stenosis in patients with duodenal ulcer, and this hypersecretion, which is associated with pyloric obstruction, might explain the incidence of duodenal ulceration as well as the occasional gastric ulcer. Hyperactivity of the antral phase of gastric secretion, which would occur in the presence of pyloric obstruction,[12] has been incriminated as the cause of gastric as distinct from duodenal ulcer.[13] It would be interesting to ascertain by experiment whether a state of hypersecretion is in fact a common finding in adult patients suffering from this disease.

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DANGERS OF EXPLORING CAVES

The tragic death of a pot-holer in Peak Cavern at Castleton, Derbyshire, has focused attention on the most obvious danger of exploring caves, that of becoming inextricably wedged, but, surprisingly, this is the first recorded fatality from this cause in Great Britain. It emphasizes the basic rule of caving: never enter any hole or passage unaccompanied or without adequate safety precautions, such as life-lines.

A hazard often assumed to exist in caves, but which in fact is extremely rare, is the presence of noxious or explosive gases. Methane and sulphuretted hydrogen have been recorded in a few instances, though in very small proportions, and are not known to have caused any accidents. Carbon dioxide occasionally accumulates by natural means at the lower ends of unventilated passages, though this again is rare, most caves being well ventilated by running water causing turbulence in the air. Indeed, there is no recorded case in a British cave of an accident directly attributed to the presence of carbon dioxide. However, it may often increase when several persons enter a confined passage or chamber, and undoubtedly it hampered rescue attempts in Peak Cavern.

Most of the dozen or so fatal accidents recorded in Britain have been due to the danger common to all outdoor pursuits—exhaustion and exposure. Most of our British caves have streams, lakes, or thick mud, in which the explorer is soon soaked. Even without these, the air is humid and everything is cold and wet. Temperatures rarely rise above 50° F. (10° C.), and the cold can soon strike chill, particularly to anyone having to wait about, however well clad. Several hours' hard work climbing down the cave may often be followed by inactivity for half an hour or so, and, unless one is fit and used to this, physical endurance can be weakened quite suddenly, even to the point where the victim is virtually unable to help himself out of the cave. It is common in such cases for morale to be suddenly lowered by the realization that the hardest work is yet to come, the task of climbing up out of the cave. Such are the circumstances which can lead to a fall, whether it is just a trip over a rock resulting in a sprained ankle, or a sheer drop from a swaying rope ladder. And the injured man, who can do little to help himself, must wait, cold and wet, until help arrives—which may take several hours. Even then the journey out may be long and arduous. The obvious first-aid measure of keeping the injured man warm and dry is not easy in a cave.

Flooding, due to heavy rainfall while the explorer is underground, brings its own dangers. He may be trapped above water-line in inner parts of the cave if the entrance passages become flooded. Usually he can only wait until the waters recede, but two or three days' wait in cold, wet conditions with little or no food could easily take its toll. Fortunately, no fatality has occurred from this cause in Britain, though people have been trapped on several occasions. A case in Switzerland a few years ago resulted in five deaths owing to an ill-judged attempt to get out through the entrance passages before the water rose too high. Diving with the help of

breathing apparatus in submerged caves can bring all the hazards common to diving and the fact that often the diver cannot surface when in difficulties.

Overseas caving has several hazards not present in Britain. A variety of animals may inhabit the cave entrance, notably snakes and scorpions; occasionally in the inner parts of some Pyrenean caves bears may be encountered. Some caves in the lower latitudes are, in contrast to those in Britain, very dry, and severe cases of dust pneumonitis have been recorded in America. Moreover, an air-borne fungus in some Central American caves causes histoplasmosis. Caves the world over are used as repositories for dead animals and miscellaneous rubbish. The explorer may contract septic wounds from scratches, and the neighbouring water supply from springs can also become polluted.

Caving accidents invariably make the headlines because of the difficulty of rescue, but, in view of the large numbers of people who go exploring pot-holes, caving is probably safer than crossing a main road. Hundreds of novice cavers go underground every week-end—schoolboys, Scouts, students, and so on. Some go for the sporting interest, some for the physical exercise, others for scientific reasons, and many for the pleasure of getting soaked and muddy. Most, fortunately, go in the company of experienced friends. But occasionally this in itself can lead to trouble, because a few novices, with the example of an expert before them, will not admit when they have had enough. When they eventually do give in, all the problems of a rescue follow. On the other side, some "experts" may fail to recognize symptoms of exhaustion in the novices they are leading.

LUPUS AND THE LIVER

In 1950 J. Waldenström[1] drew attention to some of the unusual features of cirrhosis of the liver in young adults, mainly females. Later observers[2] have confirmed these findings, and particular interest has been focused on cases of jaundice with apparent well-being, very high serum levels of gamma-globulin with positive flocculation tests, and some features suggesting adrenal hyperfunction, such as acne, hirsuties, striae, and facial mooning. Arthralgia, bouts of pyrexia, and lesions of the serious membranes are also sometimes present.

The occasional presence of L.E. cells has been noted in this type of liver disease,[2 3] a finding that is difficult to interpret. It has been suggested that these patients with chronic liver disease and L.E. cells are suffering from disseminated lupus erythematosus (D.L.E.). Reports of a favourable response to steroid drugs in some cases, and evidence of disease in other organs such as the kidney, skin, and colonic mucosa,[4 5] are thought to be further evidence in support of this concept. Against such a hypothesis is the fact that serious hepatic disease is unusual in true D.L.E., while the administration of apresoline[6] and the occurrence of sensitivity reactions to penicillin and other substances[7] are known to be associated with a positive L.E. test. Presumably these reactions are distinct from D.L.E. It may be that the positive L.E.-cell phenomenon in young patients with chronic liver disease indicates the production of tissue antibodies, and that hepatic damage and lesions in other organs represent the results of an auto-immune disease.[8] Support for this concept of continuous tissue damage from antibodies in chronic liver disease comes from the finding of positive complement-fixation tests against liver and other tissues in some patients.[9] The positive L.E.-cell phenomenon may then represent antibody formation against leucocytes. Whether this state of affairs exists and what relation it bears to the production of the D.L.E. syndrome is a source of speculation.

Recently L. G. Bartholomew and his colleagues[10] have described seven more patients with chronic liver disease and a positive L.E.-cell test. In some of these patients the clinical picture suggested that D.L.E. existed before the hepatic lesion became clinically apparent. These workers therefore feel that they have proof that the lesion they describe represents D.L.E. It would be of interest, however, before linking these diseases too closely, to know how often patients of this type exhibit a negative L.E.-cell test, for positive tests are as a rule only weakly positive.[11] Some observers[12] find that in cirrhosis of the liver the L.E.-cell test is rarely positive. The significance of the association is still obscure, and it is not known if the course of the liver lesion or its response to treatment with steroid drugs is altered in any way. Perhaps our concept of D.L.E. needs changing so that a variety of grades of the disorder are recognized, varying from a severe disease of many organs to one where the damage is predominantly in one organ, such as the liver.

[1] Waldenström, J., *Sonderband: XV. Tagung Bad Kissengen*, 1950, p. 8.
[2] Bearn, A. G., Kunkel, H. G., and Slater, R. J., *Amer. J. Med.*, 1956, **21**, 3.
[3] Joske, R. A., and King, W. E., *Lancet*, 1955, **2**, 477.
[4] Gray, N., Mackay, I. R., Taft, L. I., Weiden, S., and Wood, I. J., *Amer. J. dig. Dis.*, 1958, **3**, 481.
[5] Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H., *Medicine (Baltimore)*, 1954, **33**, 291.
[6] Morrow, J. D., Schroeder, H. A., and Perry, H. M., *Circulation*, 1953, **8**, 829.
[7] Walsh, J. R., and Zimmermann, H. J., *Blood*, 1953, **8**, 65.
[8] Burnet, F. M., and Fenner, F., *The Production of Antibodies*, 1949, Melbourne.
[9] Gajdusek, D. C., *Nature (Lond.)*, 1957, **179**, 666.
[10] Bartholomew, L. G., Hagedorn, A. B., Cain, J. C., and Baggenstoss, A. H., *New Engl. J. Med.*, 1958, **259**, 947.
[11] Mackay, I. R., Taft, L. I., and Cowling, D. C., *Lancet*, 1959, **1**, 65.
[12] Wilkinson, M., and Sacker, L. S., *Brit. med. J.*, 1957, **2**, 663.

MYSTERIOUS DENTINE

Dentine is an exceedingly interesting tissue. It is present in nearly all vertebrates, and, while its presence is restricted to the teeth in terrestrial animals, it is also found in the fossilized scales of early fish. In fact what seems to be the remains of dentine has been found in the earliest-known vertebrates from the Ordovician Colorado beds of approximately 400 million years ago. Tubular dentine differs from bone in that it is acellular and avascular, and, though much work has been done on it, several basic problems, particularly relating to its formation, nutrition, and nerve supply, remain unsolved. W. Warwick James has presented a masterly survey[1] of this field. With a series of beautiful photomicrographs he shows the basic similarity of tubular dentine in fish, amphibians, reptiles, and mammals; he draws the conclusion that tubular

[1] James, W. W., *Trans. zool. Soc. Lond.*, 1957, **29**, 1.
[2] Sir John Tomes: 1836-95; English dental surgeon who carried out important researches into the structure of dental tissues as well as being pre-eminent in the practice of his profession.

dentine apparently precedes other forms of dentine, but suggests that further work is necessary in correlating its relationship to other forms of dentine and to bone.

Fully developed tubular dentine, being acellular and having a low metabolic interchange, is more inert than other calcified connective tissues. For many years it has been generally held that the tubules in the dentine contained so-called Tomes's fibrils[2] — elongated protoplasmic processes extending from the odontoblast cells. But whether these fibrils filled the tubules or were surrounded by a space filled with tissue fluid was a matter for argument. Warwick James suggests that the odontoblasts should be regarded as fibrogenetic cells forming the matrix, and that in fact no protoplasmic fibrillar extension into the tubule from the odontoblast cell exists, the appearance of a fibril being due to coagulated colloidal components of the tissue fluid. This hypothesis that tubular dentine is composed of a matrix permeated by tubules containing tissue fluid without the presence of cytoplasmic processes has the merit of aligning it more closely with other forms of connective tissue.

A matter of great interest to the patient, as well as to the clinician and research worker, is the sensitivity of dentine. Much work has been done on the problem of its innervation, but so far nerve fibrils have been traced only from the pulp into the predentine and a very short way into the formed dentine. No nerve endings have been detected in the dentine under the enamel, though this area is known to be one of high sensitivity. It has been suggested that pressure or osmotic stimulus is transmitted down the tissue fluid, or fibril, if one is present, in the dental tubule to the rich plexus of nerves in the odontoblast area of the dental pulp. Warwick James stresses the possible importance of the elasticity of the dentine as a factor in the transference of pressure and hence pain, but evidently more work is needed on these controversial problems. Meanwhile this is a stimulating contribution to knowledge in a field where zoologists, dental histologists, and clinicians should meet more often.

GLYCYRRHETINIC ACID OINTMENT

In 1950 a report by J. A. Molhuysen and colleagues[1] showed that an extract of liquorice had some properties like those of A.C.T.H., chiefly in the retention of water, chloride, and sodium, mediated by the suprarenal. Administration of this extract in one case of rheumatoid arthritis failed to show any anti-inflammatory effect. It was hardly to be expected from this that liquorice extracts would have an anti-inflammatory action when applied to the skin surface, but such a preparation—glycyrrhetinic acid—has been reported to possess these properties.

A series of brief clinical reports on glycyrrhetinic acid ointment appeared in our correspondence columns during the second half of 1956 and the first part of 1957. The authors of some of these[2–6] found glycyrrhetinic acid ointment notably inferior to hydrocortisone ointment or no better than the base used as a blind control. On the other hand Q. Evans[7] found glycyrrhetinic acid as good as hydrocortisone, and J. Sommerville[8] obtained apparently favourable results in some cases.

The largest clinical series published about this time was that of E. Colin-Jones and G. F. Somers,[9 10] who recorded the treatment of 254 cases with this substance and claimed benefit in the great majority, equal to that obtained with hydrocortisone ; control comparisons were relatively few, and the trials were apparently not of the " blind " variety. A recent investigation of H. T. H. Wilson and J. H. Edwards[11] has avoided this pitfall. They compared hydrocortisone and glycyrrhetinic acid ointments on 29 patients by a blind-controlled cross-over method, and hydrocortisone emerged as greatly superior. This follows close upon the report of a trial by B. B. Jørgensen,[12] who witnessed considerable deterioration among his controls and over the whole of a series of 43 cases could not establish that glycyrrhetinic acid was superior to a placebo.

This tantalizing inconsistency suggests various possible explanations. First, it emphasizes the need for clinical trials to be carefully controlled experiments, thought out and designed beforehand, with a proper system of selection of control subjects. Second, Colin-Jones and Somers emphasize that all substances called glycyrrhetinic acid are not necessarily the same. The variety they used has also been shown to have anti-inflammatory hydrocortisone-like effects in animal experiments ; Wilson and Edwards used a different product : Jørgensen used yet another. But Warin and Evans used the same as Colin-Jones and Somers, yet found it no better that the control base alone—which incidentally produced some benefit, as any emollient may do. Most of the reports mentioned here do not specify the origin of the glycyrrhetinic acid their authors used, and it is not certain that they were all using the same substance. At present, therefore, it is impossible to be certain of the merits, if any, of glycyrrhetinic acid in dermatology. The investigation carried out by Wilson and Edwards seems to be of the most thorough and convincing nature. But further properly designed investigations with the various preparations available are still required before they can be recommended for routine use or before they can be finally discarded as ineffective.

We record with deep regret the death on March 30 of Sir Robert Muir, F.R.S., the eminent pathologist, in his 95th year. He held the chair of pathology at the University of Glasgow from 1899 to 1936.

Professor Robert Platt was re-elected President of the Royal College of Physicians of London on March 23.

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[1] Molhuysen, J. A., *et al.*, *Lancet*, 1950, **2**, 381.
[2] Warin, R. P., and Evans, C. D., *Brit. med. J.*, 1956, **2**, 480.
[3] Bettley, F. R., ibid., 1956, **2**, 882.
[4] Russell, B., ibid., 1956, **2**, 1113.
[5] McCallum, D. I., ibid., 1956, **2**, 1239.
[6] Hall, R., and Jefferson, J., ibid., 1956, **2**, 1431.
[7] Evans, Q., ibid., 1956, **2**, 1239.
[8] Sommerville, J., ibid., 1957, **1**, 282.
[9] Colin-Jones, E., and Somers, G. F., *Med. Press*, 1957, **238**, 206.
[10] —— *Brit. med. J.*, 1957, **1**, 161.
[11] Wilson, H. T. H., and Edwards, J. H., *Brit. J. Derm.*, 1958, **70**, 452.
[12] Jørgensen, B. B., *Acta derm.-venereol.* (*Stockh.*), 1958, **38**, 189.

Drug Treatment of Disease

ADDICTION TO DRUGS: PART II*

BY

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Treatment of Addiction

There are three underlying principles. The first is to wean the patient from the drug. The second is to persuade him of the necessity of forswearing it finally and for ever The third is for both patient and therapist to try to understand the mode of life, the attitudes of mind and the "psychodynamics" that have led to the addiction, and, in the light of that understanding, to make adjustments in the mode of life and attitudes of mind, with the substitution of other sources of satisfaction. The first of these principles may be effected without much difficulty provided the patient agrees, but implementation of the second and third principles is never easy and may be very difficult indeed. It is, however, with the first principle that we are mainly concerned here.

It is almost always necessary for the patient to be removed from home and from the associations with which the addiction started, and placed in a controlled environment (i.e., hospital or nursing-home), away from sources of supply. Even so, many patients will cheat, and precautions must be taken accordingly. The patient should be kept in bed, on a full diet with extra glucose fluids and vitamins. Occupation should be encouraged as soon as the patient's condition allows. Daily charts should be kept.

The means by which the drug is withdrawn will depend upon the severity that may be expected of the withdrawal symptoms. Severe withdrawal symptoms may be expected in addiction to morphine and its derivatives, to methadone and phenadoxone, and to pethidine. Moderate withdrawal symptoms may be expected in gross barbiturate addiction. Otherwise the withdrawal symptoms will be mild. The milder the withdrawal symptoms, the stronger is the case for immediate withdrawal of the drug—for example, in alcoholism, and in addiction to cocaine, chloral, and amphetamine. As to the more severe addictions, it is sometimes argued that gradual withdrawal by tapering off the dose is only to prolong the agony, but, since few patients will agree to abrupt withdrawal and it is possible to conduct gradual withdrawal without agony, the latter seems the better course. At this point it may be borne in mind that the addict's usual tendency to understate the amount that he takes is now apt to be reversed, owing to fear of being cut off too soon. A plan is then formed by which the dose of the addictive drug is gradually reduced over a period of, say, five to six days until an exiguously small dose is reached, followed by none at all. Formerly, it was usual to substitute barbiturates, and to induce a light narcosis to mitigate the discomfort of withdrawal. Nowadays this can be more satisfactorily managed by the use of chlorpromazine ("largactil," "thorazine") or its relatives, promazine hydrochloride ("sparine") and acetylpromazine ("notensil"). These substances are also useful in the treatment of barbiturate addiction itself.

For example, a patient with a combined addiction to morphine and pethidine had succeeded in reducing her consumption of the former to about 1/10 gr. (6.5 mg.) three times a day, and of the latter to about 400 mg. in the day, usually taken in about eight doses varying between 40 mg. and 100 mg. each. The regime outlined in Table I was successful in getting her off the admittedly small doses of both drugs over a period of eight days with virtually no discomfort at all.

Such plans must not be adhered to too rigidly. There should be elasticity and variation according to the needs of the case. Anorexia, for example, may be so marked that the patient cannot eat satisfactorily unless the drug of addiction is given in relation to meals. Much discomfort may call for increase in dosage of chlorpromazine or barbiturate. The former is to be preferred. It may be given intramuscularly if a rapid effect is required, otherwise by mouth, in doses of 50–100 mg., which may be repeated if necessary up to three, four, or more times in the day. In the dosage that is likely to be required for treating drug addiction, such untoward

TABLE I

	Time	Pethidine	Morphine	Chlorpromazine	Barbiturates
1st day	0500	75 mg.	—	—	—
	0800	50 ,,	gr. 3/40 (5 mg.)	—	—
	1030	50 ,,	—	—	—
	1500	50 ,,	—	—	Amylobarbitone gr. 3/4 (50 mg.)
	1900	100 ,,	—	—	—
	2230	50 ,,	—	—	Sod. amylobarb. gr. 6 (400 mg.)
		375 ,,			
2nd day	0730	50 ,,	—	—	—
	1030	50 ,,	—	50 mg. i.m.*	—
	1500	25 ,,	—	—	—
	1900	75 ,,	—	50 mg. i.m.	—
	2230	50 ,,	—	—	Sod. amylobarb. gr. 6 (400 mg.)
		250 ,,			
3rd day	0730	50 ,,	—	—	—
	1030	25 ,,	—	50 mg. i.m.	—
	1500	25 ,,	—	—	—
	1900	50 ,,	—	50 mg. i.m.	—
	2230	50 ,,	—	—	Sod. amylobarb. gr. 6 (400 mg.)
		200 ,,			
4th day	0730	50 ,,	—	—	—
	1030	25 ,,	—	—	—
	1500	—	—	50 mg. i.m.	—
	1900	50 ,,	—	—	—
	2230	25 ,,	—	—	Sod. amylobarb. gr. 6 (400 mg.)
		150 ,,			
5th day	0730	25 ,,	—	50 mg. i.m.	—
	1030	25 ,,	—	—	—
	1500	—	—	50 mg. i.m.	—
	1900	25 ,,	—	—	—
	2230	25 ,,	—	—	Sod. amylobarb. gr. 6 (400 mg.)
		100 ,,			

The pethidine was then reduced to 25 mg. t.d.s. and 25 mg. b.d. on successive days before being stopped altogether on the eighth day, when chlorpromazine 50 mg. t.d.s. was substituted without complaint from the patient.
* i.m. = intramuscularly.

*Part I of this article was published last week at p. 850.

TABLE II

	Time	Heroin	Chlorpromazine	Barbiturate (Sod. Amylobarb.)	Paraldehyde
1st day	1600	gr. 2/3 (45 mg.) i.m.*	—	—	11 ml.
	1900	gr. 5/12 (27 mg.) i.m.	25 mg.	—	—
	2200	gr. 5/12 (27 mg.)	—	gr. 6 (400 mg.)	—
2nd day	0800	—	50 mg.	gr. 2 (130 mg.)	—
	0900	gr. 3/4 (50 mg.) i.m.	—	—	—
	1300	gr. 5/12 (27 mg.)	—	gr. 2 (130 mg.)	—
	1600	gr. 5/12 (27 mg.)	—	—	11 ml.
	1900	gr. 5/12 (27 mg.)	50 mg.	—	—
	2200	gr. 5/12 (27 mg.)	—	gr. 6 (400 mg.)	—
3rd day	0800	gr. 6/12 (32 mg.)	50 mg.	gr. 2 (130 mg.)	—
	1300	gr. 2/12 (11 mg.)	25 mg.	—	—
	1600	gr. 2/12 (11 mg.)	50 mg.	—	—
	1900	gr. 2/12 (11 mg.)	25 mg.	—	—
	2200	gr. 2/12 (11 mg.)	—	gr. 6 (400 mg.)	—
4th day	0700	gr. 4/12 (22 mg.)	—	—	—
	0800	—	50 mg.	gr. 2 (130 mg.)	—
	1300	gr. 2/12 (11 mg.)	25 mg.	—	—
	1600	gr. 2/12 (11 mg.)	50 mg.	—	—
	1900	gr. 2/12 (11 mg.)	25 mg.	—	—
	2200	gr. 2/12 (11 mg.)	—	gr. 6 (400 mg.)	—
5th day	0700	gr. 4/12 (22 mg.)	—	—	—
	0800	—	50 mg.	gr. 2 (130 mg.)	—
	1300	gr. 1/12 (5 mg.)	25 mg.	—	—
	1600	gr. 1/12 (5 mg.)	50 mg.	—	—
	1900	gr. 1/12 (5 mg.)	25 mg.	—	—
	2200	gr. 1/12 (5 mg.)	—	gr. 6 (400 mg.)	—
6th day	0700	gr. 3/12 (16 mg.)	—	—	—
	0800	—	50 mg.	gr. 2 (130 mg.)	—
	1300	gr. 1/12 (5 mg.)	25 mg.	—	—
	1600	—	50 mg.	—	—
	1800	gr. 1/12 (5 mg.)	—	gr. 2 (130 mg.)	—
	2200	gr. 1/12 (5 mg.)	—	gr. 6 (400 mg.)	—

The patient was off heroin by the eighth day without discomfort, but this withdrawal could have been achieved far more quickly if the doses of chlorpromazine had been doubled.
* i.m. = intramuscularly.

side-effects as jaundice, skin rashes, and development of a Parkinsonian syndrome are unlikely to occur, but, if there is a history of previous jaundice or evidence of liver damage, the allegedly less toxic related compounds—for example, promazine hydrochloride—may be substituted in similar dosage.

The plan shown in Table II allowed a comfortable withdrawal in the case of a man addicted to upwards of 3 gr. (200 mg.) of heroin intravenously spread through the day.

A patient addicted to morphine for seven years and accustomed to between twenty and thirty tablets of ¼ gr. (16 mg.) each in the day, was given ½ gr. (32 mg.) hypodermically with sodium amylobarbitone 6 gr. (400 mg.), when admitted late at night, and thereafter was weaned from the drug with practically no complaint, though she was a very querulous person (see Table III).

Apart from giving chlorpromazine or its related compounds together with barbiturates, a comparatively modern technique which may be combined with that is treatment with insulin. The patient may be given 20 units, increased to 30 and then 40 on successive days, subcutaneously at, say, 7 a.m. This is followed by a meal rich in carbohydrate three hours later. The procedure can be repeated in the afternoon. (The patient should be observed day and night for possible subsequent hypoglycaemic reactions, which will call for reduction of insulin dosage). If the patient shows any sign of slipping towards sleepiness before three hours have elapsed, the hypoglycaemia should be terminated by glucose fluids, if necessary by nasal tube or by 33% glucose intravenously. Again, the next dose of insulin should be smaller. This is known as modified insulin treatment.

When withdrawal symptoms can be expected to be moderate or mild—that is, cases of addiction to barbiturates, alcohol, cocaine, chloral, amphetamine, or paraldehyde—the administration of chlorpromazine or its related compounds in doses of, say, 50 mg. four times a day orally (with intramuscular injections periodically instead, if rapidity of effect is specially desired), should suffice to keep the patient comfortable, and can be reduced gradually over several days after the patient has been weaned from the addictive drug itself. The hazard of pre-existent liver damage should be borne in mind, however, especially in alcoholic patients, whose withdrawal symptoms are anyway unlikely to be so severe as to call for any substantial medication unless there is a serious threat of delirium tremens.

Alcoholic Addiction

The treatment of alcoholic addiction is in itself a large subject, but it is worth mentioning here that both chlorpromazine (or the allied promazine) and the so-called modified insulin treatment described above are of use in controlling delirium tremens, while modified insulin is also valuable for detoxicating the alcoholic patient who remains short of delirium. Apart from detoxication and the control of delirium tremens, the immediate treatment of chronic alcoholism is usually directed towards diminishing the craving for and setting up an aversion to alcohol. These are specialized techniques which have often been described in the textbooks.

What is comparatively new is the long-term treatment of the alcoholic with disulfiram ("antabuse," "cronetal"). This substance, taken by mouth, interferes with the normal metabolism of ingested alcohol, causing accumulation in the blood stream of acetaldehyde, with unpleasant toxic effect. In fact, it causes acetaldehyde poisoning, with symptoms of tightness in the chest, pounding in the neck, a burning flush, headache, profound malaise, sometimes with nausea and

TABLE III

	Time	Morphine	Chlorpromazine	Barbiturate (Sod. Amylobarb.)	Paraldehyde
1st day	0800	gr. ½ (32 mg.)	50 mg. orally		
	1200	gr. ½ (32 mg.)	—		
	1600	—	50 mg. i.m.*		
	1800	gr. ¼ (16 mg.)	—		
	2200	gr. ½ (32 mg.)		gr. 6 (400 mg.)	
2nd day	0800	gr. ¼ (16 mg.)	50 mg. i.m.		
	1200	gr. ½ (32 mg.)	—		
	1600	—	50 mg. i.m.		
	1800	gr. ¼ (16 mg.)	—		
	2200	gr. ½ (32 mg.)	—	gr. 6 (400 mg.)	
3rd day	0800	gr. ¼ (16 mg.)	50 mg. i.m.		
	1200	gr. ¼ (16 mg.)	25 mg. orally		
	1600	—	50 mg. orally		
	1800	gr. ¼ (16 mg.)	—		
	2200	gr. ½ (32 mg.)	—	gr. 6 (400 mg.)	
4th day	0800	gr. ¼ (16 mg.)	50 mg. i.m.		
	1200	gr. ¼ (16 mg.)	50 mg. orally		
	1600	—	50 mg. orally		
	1800	gr. ⅛ (8 mg.)	—		
	2200	gr. ¼ (16 mg.)	—	gr. 6 (400 mg.)	
5th day	0800	gr. ¼ (16 mg.)	50 mg. orally		
	1200	gr. ⅛ (8 mg.)	25 mg. orally		
	1600	—	50 mg. orally		
	1800	gr. ⅛ (8 mg.)	—		
	2200	gr. ⅛ (8 mg.)	—	gr. 6 (400 mg.)	
6th day	0800	gr. ⅛ (8 mg.)	50 mg. orally		
	1200	—	50 mg. i.m.		
	1600	—	—		6 ml. i.m.
	1800	gr. ⅛ (8 mg.)	—		
	2200	gr. ¼ (16 mg.)	—	gr. 6 (400 mg.)	

Two days later the patient was morphine-free. Again, the withdrawal could have been achieved more quickly with larger doses of chlorpromazine.
* i.m. = intramuscularly.

vomiting. The rapidity and extent of these developments depend upon the rapidity of ingestion of alcohol and upon the amount of disulfiram taken. They may progress to orthostatic faintness and vasomotor collapse; coronary thrombosis has been known to occur. For these reasons disulfiram should never be given to an intoxicated patient, and introduction to the treatment is best given in hospital. It is usual to give 1–2 g. of disulfiram daily for three days, and to give the patient alcohol, in its preferred form, on the fourth day. A suitable dose is 2 fl. oz. (57 ml.) of gin or whisky, which may be repeated every 10–20 minutes according to the effect or lack of it. The flushing is usually replaced by pallor after about 45–60 minutes, and it is safest then to discontinue the alcohol, usually with the patient's ready agreement. The early development of pallor, with rising pulse rate and falling blood pressure, is a warning signal. As delayed reactions with vasomotor collapse and vomiting sometimes occur, the patient should be kept under observation for the rest of the day, and preferably in bed. If the effect is not severe enough to make much impression on the patient, the procedure can be repeated with larger and more frequent doses of alcohol. The patient is then encouraged to continue taking disulfiram (0.25 g.) daily in the hope that knowledge of its effects may help him to abstain from alcohol. No great reliance can be placed on this form of treatment exeept as a useful adjuvant to the more rigorous methods already referred to, designed to remove the craving and set up an aversion.

Finally, since all addictions, and especially alcoholism, are apt to lead to dietary neglect, vitamins will have a part to play in treatment. Although I am less impressed than many by the effect of massive vitamin dosage in controlling or aborting delirium tremens, this may confer benefit and appears to do no harm. Recommended doses are: aneurine 1,000 mg., riboflavine 10 mg., pyridoxine 400 mg., nicotinic acid amide 200 mg., ascorbic acid 1,500 mg. These are best given intravenously, and, if the patient can be kept quiet enough, can be added to an intravenous infusion of 1,000–2,000 ml. of 10% dextrose in normal saline containing also 30 units of insulin. Except in cases of delirium tremens, a suitable preparation of vitamins for correcting dietary deficiency and stimulating appetite during the withdrawal phase is "parentrovite." This is prepared in ampoules for intravenous injection. One or more ampoules a day may be given according to the nutritional state.

FROM SCHOOL TO UNIVERSITY

EDUCATIONISTS CONFER AT LEEDS

A conference on "School and University Relationships, with Particular Reference to Medicine," was held last week at Leeds under the auspices of the Institute of Education of the University of Leeds. About seventy headmasters, headmistresses, and members of the faculty of medicine attended.

The conference was opened by Professor P. J. MOIR, dean of the faculty of medicine, who gave a brief account of the landmarks of medical training, the opportunities available to medical graduates, and the current distribution of medical graduates in the different branches of the profession. Figures relating to women were given, based on a report of the British Medical Women's Federation.

Professor A. HEMINGWAY, professor of physiology, stressed the unique feature of medical training, in that it combined both university education and vocational training. Explaining the role of the General Medical Council in the control of medical education, he stressed that the G.M.C. made recommendations and that these were not to be interpreted as regulations. The recent report of the G.M.C. was couched in general terms and gave the universities much greater freedom to plan courses. A new development, resulting from the passing of the Medical Act of 1951, had been the power of the G.M.C. to inspect medical schools and to report upon the courses, teaching, and equipment.

The speaker then passed to the requirements for entry into medical faculties. In 1957 2,192 medical students were admitted to the medical schools of Great Britain, and of these 1,456 took a 1st M.B. course. Therefore, roughly one-third of those admitted were exempted from the 1st M.B. The new entrance requirements of London University—three subjects at the advanced level in the G.C.E. (chemistry, physics, and zoology in the case of medicine)—had had a profound effect upon the policy of other universities. Professor Hemingway himself did not personally approve of modern tendencies, nor in the partial disappearance of the 1st M.B. in the universities. In discussing university entrance requirements, he thought that there was the tendency to neglect the quantitative approach to medicine, and he hoped that schoolmasters would realize that a good grounding in mathematics and physics provided a useful basis upon which to build a medical course.

A Schoolmaster's View

Mr. J. DRONFIELD, headmaster of St. Peter's School, York, spoke as a schoolmaster concerned with the problem of advising boys upon medicine as a career and then with getting them into medical schools. He held the profession in high regard, as in his view did the public. Even the hardened businessman was not altogether disappointed if one of his sons, not wishing to enter the business, was prepared to take up medicine. He had been interested in the recent return to popularity of medicine as a career for doctors' sons.

The qualities he looked for in advising a boy to study medicine were (1) a good intelligence, (2) an interest in people, and (3) that he was a good mixer. He took notice of a sense of vocation, but in a boy of 16 or 17 this could often be misleading, and one had to be very careful in interpreting the significance of a boy's so-called sense of vocation. The schools wanted to know how much science a boy ought to know before beginning the study of medicine and how much time should be spent on non-vocational subjects.

Women in Medicine

Miss M. M. BLACK, headmistress of Bradford Girls' Grammar School, opened the discussion from the woman's point of view. Medicine was a very long course for a woman to undertake. When the average age of marriage was lower, there was a tendency for girls to feel they were "on the shelf" if they were not engaged by the age of 19. This often meant that they married during the medical course, which was far from being an ideal situation. Miss Black asked if the supposed equality of men and women in medicine really was a fact when it came to appointments. She would like to know whether women gravitated towards

certain branches of medicine because of aptitude or because they were unable to find openings in the branches they wished to follow.

Need for Continued Education

Professor R. E. TUNBRIDGE emphasized the changing social pattern and organization of medicine, the impact of rapid advances of medical knowledge upon training, and the increasing realization of the need for continued education throughout the whole of a medical man's life. Postgraduate education was almost rudimentary in this country, and there was a need to provide for refresher courses for all medical graduates at least every five years. He thought this had a bearing on the content of the course, and he also stressed the serious educational disadvantages of the present long course—six years of medical training, one year as a pre-registration house officer, and two years in the Services.

It was generally agreed that in most professions the years immediately following the first degree, from the age of 21 to 25, were the most formative years in the training of the leaders of a profession. In the National Health Service at the present time it was very serious that a medical graduate was often 27 or 28 before he was free to begin serious postgraduate study.

Professor Tunbridge stressed the need for dividing the medical course into a university phase and a vocational phase, and suggested that there was much to be said for taking a degree in general science rather than the 2nd M.B. as at present constituted. Whatever branch of practice a person undertook he must be thoroughly educated in the basic sciences if he was to deal with the enlightened and better-educated public of to-morrow. The advantages of taking a general degree are that it would provide openings in many professions and would permit the selection of candidates for vocational training in medicine at a much more mature age.

Professor G. P. MEREDITH discussed the difficulties of assessment and selection in medicine. The varieties of openings, once a person was qualified, made any question of job analysis impossible. Furthermore, ability was not readily assessed. During his long course of study the student was subject to a multitude of influences, almost all of which were unpredictable, so that it was impossible to say with certainty how a student might develop ten years hence.

Mr. J. S. BARNSHAW, headmaster of West Leeds High School, took up the problem of general education and the difficulty for the schools when the children had little or no educational home background. Reference had been made to the students who, on arriving at the university, sat back and expected to be taught everything: this was not a new experience to a schoolmaster, for it often happened to those who had been successful in the 11+ examination.

During a lively discussion many familiar topics were raised—the poor standard of English, the discrepancy between the entrance requirements for different universities, the university dichotomy of approach in asking for more science on the one hand and more general culture on the other, the need for the universities to look after the students' welfare, the staffing and other problems in the schools, the staffing of peripheral hospitals, and the maldistribution of members within the profession.

Mr. A. M. KEAN, the deputy director of the Institute of Education, thought the discussion could be summarized under three headings: (1) the problems facing students entering medicine, (2) the general question of the relationship between the universities and the schools, and (3) administrative problems, such as the need for consistency in the giving of grants (the policy of some local authorities not to give grants for the 1st M.B. course was unfortunate). He also thought there was need for consideration of the regulations for admission, the question of the amount of science necessary on leaving school, and the relationship between what the universities required and what the schools are capable of doing.

APPROVED NAMES

The last supplement to the consolidated list of "approved names" was published in the *Journal* of January 31, 1959 (p. 298). A new supplement, dated March, 1959, is printed below. Communications relating to "approved names" should be addressed to the secretary, British Pharmacopoeia Commission, General Medical Council, 44, Hallam Street, London, W.1.

Approved Name	Other Names	Notes
Azapetine ..	1-Allyl-2: 7-dihydro-3: 4-5: 6-dibenzazepine "Ilidar" is the phosphate	Peripheral vasodilator
Calcium benzamidosalicylate	Calcium 4-benzamido-2-hydroxybenzoate "Aminacyl B-PAS"; "therapas"	Antituberculosis drug
Dexamethasone	9α-Fluoro-11β: 17α: 21-trihydroxy-16α-methylpregna-1: 4-diene-3: 20-dione 9α-Fluoro-16α-methylprednisolone "Decadron"; "deronil"; "dexacortisyl" is the 21-acetate	Corticosteroid
Dimenoxadole ..	2-Dimethylaminoethyl α-ethoxy-αα-diphenylacetate	Analgesic
Ditophal ..	Diethyl dithiol*iso*phthalate "Etisul"	Antileprotic drug
Fluopromazine	10-(3-Dimethylaminopropyl)-2-trifluoromethylphenothiazine "Vespral" is the hydrochloride; "vesprin" is the hydrochloride	Treatment of schizophrenia and other mental disorders
Hydrochlorothiazide	6-Chloro-3: 4-dihydro-7-sulphamoyl-benzo-1: 2: 4-thiadiazine 1: 1-dioxide "Esidrex"; "hydro-saluric"	Oral diuretic
Hydroflumethiazide	3: 4-Dihydro-7-sulphamoyl-6-trifluoromethylbenzo-1: 2: 4-thiadiazine 1: 1-dioxide "Hydrenox"; "naclex"; "rontyl"	" "
Mebhydrolin ..	5-Benzyl-1: 2: 3: 4-tetrahydro-2-methylpyrid-[4,3-*b*]indole "Incidal" is the naphthalene-1: 5-disulphonate	Antihistaminic
Methylchromone	3-Methylchromone "Crodimyl"	Coronary vasodilator
Norcodeine ..	*N*-Demethyl codeine	Analgesic
Normorphine ..	*N*-Demethyl morphine	"
Orphenadrine ..	2-Dimethylaminoethyl 2-methyldiphenylmethyl ether "Disipal" is the hydrochloride	Treatment of Parkinsonism
Phenmetrazine ..	Tetrahydro-3-methyl-2-phenyl-1: 4-oxazine "Preludin"	Treatment of obesity
Pipamazine ..	10-[3-(4-Carbamoylpiperidino)-propyl]-2-chlorophenothiazine	Anti-emetic drug
Prothipendyl ..	10-(3-Dimethylaminopropyl)-9-thia-1: 10-diaza-anthracene "Phrenotropin" is the hydrochloride	Treatment of psychoneuroses
Sulphasalazine ..	4-Hydroxy-4'-(pyrid-2-ylsulphamoyl)-azobenzene-3-carboxylic acid "Salazopyrin"	Treatment of ulcerative colitis
Thiambutosine ..	*N*-*p*-Butoxyphenyl-*N'*-*p*-dimethylaminophenylthiourea 4-Butoxy-4'-dimethylaminodiphenylthiourea "Ciba 1906"	Antileprotic drug
Thiotepa ..	Tri-1-aziridinylphosphine sulphide Triethylene thiophosphoramide	Anti-neoplastic drug

The Lending Library Unit of the Department of Scientific and Industrial Research has started to collect Chinese scientific literature. About 150 Chinese periodicals are now on regular order, and the first batch has arrived at the Library's London premises. This is announced in the March issue of the recently introduced *L.L.U. Translations Bulletin* (*The L.L.U Translations Bulletin*, H.M.S.O., price 4s., 4s. 5d. by post). In a special article the *Bulletin* suggests that we cannot ignore the scientific output of China, which may be growing rapidly. Already the Lending Library Unit is noted for its large collection of Russian scientific literature, which is available to research, industrial, and other organizations, through a loans service. The Library also organizes a scheme for the translation of Russian scientific literature, in collaboration with the National Science Foundation in the United States. This may possibly be extended in the future to include scientific literature from China. Meanwhile, the contents of these Chinese publications must be assessed, and a scientist with a knowledge of Chinese is being recruited by L.L.U. to select and promote use of Chinese scientific and technological literature. The Lending Library Unit in London is the nucleus of the new National Lending Library for Science and Technology, which will be set up at Thorp Arch, near Boston Spa, Yorks, in 1961.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Conspers. zinc. undecen. *B.N.F.*—Zinc undecenoate 10% and undecenoic acid 2% in powder base.

Decilderm Powder (Duncan, Flockhart).

Desenex Powder (Wallace and Tierman).

Mycota Powder (Boots).

These contain zinc undecenoate 20% and undecenoic acid 2% in powder base.

Tineafax Powder (Burroughs Wellcome).—Zinc undecenoate 10% in powder base.

Procelium Powder (Genatosan).—Zinc undecenoate 5% and sodium propionate 5% in powder base.

These fungicides are not new, but they are probably as good as most substances used for the treatment of ringworm. They have the advantage of being less likely to irritate or sensitize the skin than some antimycotic agents. In the long-term treatment of low-grade ringworm infections of the feet, and in the prevention of relapses, a powder is probably better than greasy applications. In general, the treatment of ringworm is not very satisfactory, but the formulation of these powders is reasonable. They are perhaps best administered for low-grade infections, and for the prevention of relapses after the patient has recovered from an attack or greatly improved. Used in this type of case, they may be expected to give favourable results.

N.H.S. basic price: conspers. zinc. undecen. *B.N.F.*, 2 oz., 1s. 2½d.; decilderm, 1½ oz., 2s.; desenex, 2 oz., 2s. 7½d.; mycota, 2½ oz., 1s. 8d.; tineafax, 25 g., 1s. 10½d.; procelium, 25 g., 1s. 9d.

Penitriad (May and Baker).—Each tablet contains potassium phenoxymethyl penicillin equivalent to 60 mg. of the free acid, and 167 mg. each of sulphadimidine, sulphadiazine, and sulphathiazole—that is, 100,000 units of penicillin in the form best absorbed when given orally and 0.5 g. of triple sulphonamide.

There is some evidence of synergic action between penicillin and sulphonamides, and such a combination is well suited for the treatment of pneumonia and other pneumococcal infections and of any infection due to haemolytic streptococci of Group A. Its usefulness in staphylococcal infections is doubtful, for these organisms are normally much less sensitive to sulphonamides and now often resistant to penicillin. In somewhat larger doses an effect is to be expected in infections of the air passages due to *Haemophilus influenzae*. In other Gram-negative infections except gonorrhoea, only the sulphonamide element would have an effect.

N.H.S. basic price: 250 tabs., 65s.

Medrone Tablets (Upjohn).—These are methylprednisolone in scored tablets of 4 mg.

Investigations of the clinical activity of 6-methyl-delta-hydrocortisone (methylprednisolone) as an anti-inflammatory and anti-allergic agent and as a suppressant of the activity of the adrenal cortex have been undertaken in a variety of disorders for which corticotherapy is usually indicated. It would seem that milligram for milligram medrone is nearly twice as powerful as prednisolone, so that the initial and maintenance doses of the latter should be approximately halved to calculate the dosage of medrone. While the side-effects of medrone are similar to those of other adrenal corticosteroids, they would seem to be less marked generally, and in particular medrone has been shown to have less tendency to stimulate appetite and to cause retention of water and salt. Cortisone remains the drug of choice in the replacement therapy of Addison's disease and hypopituitarism.

N.H.S. basic price: 30 tabs., 40s.

Correspondence

Blood-group Antigens and Peptic Ulcer

SIR,—It seems fairly clear from the careful researches of Dr. C. A. Clarke and his co-workers (*Journal*, March 7, p. 603) that the liability of group O subjects to duodenal ulcer is not due to H substance *in the digestive juices* protecting less efficiently than A and B substances *in these juices*. Though the significance is at the conventional level of $P<0.05$, it seems very likely that there may be a gradient in ulcer susceptibility from O non-secretor, through A, B, and AB non-secretor, and O secretor, to the relatively protected A, B, and AB secretors. This gradient could be explained on the assumption that the blood group substances not only in the digestive juices but *on or in the cells* (if indeed they are present on or in the cells of duodenal mucosa) may protect against, or cause, ulcer differentially. The ulcerogenic or protective activity of group substance on or in the cells might or might not be immunological, but it would be strange if activity of secreted group substance were different in character from an entirely separate, immunological ulcer effect of group substance in or on cells. We should not assume that the sole function of a cell-attached antigen is its antigenicity.

Two of the deductions which Clarke and his co-workers make from their analysis seem to me to require a slight qualification which is presumably implied though not stated in so many words. (1) "The hypothesis that the excess of group O in duodenal ulcers is due entirely to H substance protecting less than A or B substances is refuted. . . ." (2) [Final conclusion] "These results [i.e. the measurement of salivary fucose concentration] suggest that the protection enjoyed by ABH secretors is not due to the blood group substances protecting quantitatively." In both of these statements it would seem to me that the words "in the digestive juices" should be inserted, in the first sentence after the words "H substance," and in the second sentence after the words "blood group substances."

It may indeed emerge in due course that the different susceptibility to ulcer of subjects of different blood group is due to an immunological reaction. It is unlikely that the final explanation will be a simple one, however. In the course of these blood group studies it would be dangerous to forget the association between hyperchlorhydria and duodenal ulcer, a very much more striking relationship than that between blood group and ulcer. It should not be forgotten, too, that K. H. Køster *et al.*[1] showed an association between O and hyperacidity. It should be remembered also that D. A. P. Brown *et al.*[2] reported an O frequency of 69.67% in 79 stomal ulcers, and though their series was small their figures were significant at the $P<0.01$ level. Brown's figures not only argue with immense strength against the stratification theory, but they strongly suggest a quantitative effect of blood group substance, and longer series are obviously required both of secretor status within the various blood groups and of blood group and secretor status in respect of stomal ulcer.

Clarke and his co-workers recall that the degree of association between duodenal and gastric ulcer, and group O, varies from place to place. In Liverpool group O has an association with duodenal ulcer, but not with gastric ulcer, whereas in some other centres group O shows an association with gastric ulcer though a less notable association than with duodenal ulcer. That there should be a relationship demonstrable between duodenal ulcer and group O, yet no relationship between gastric ulcer and group O, is extremely surprising, if all gastric ulcers are included in one group.

As Daintree Johnson[3] has shown, gastric ulcers can be grouped into three varieties: (1) the lesser curve and posterior wall ulcers of the stomach; (2) the gastric ulcer occurring in combination with duodenal ulcer; (3) the pre-pyloric ulcer. In Johnson's second type the gastric ulcer almost invariably is secondary to a duodenal ulcer, and the pre-pyloric ulcer of type three seems in its genesis and its behaviour to resemble a duodenal ulcer. In a random group of gastric ulcers some proportion of the patients would have their ulceration in a pre-pyloric situation or would have the gastric ulcer as a complication of primary duodenal ulcer. It is probable that this proportion of combined or pre-pyloric ulcers would vary in fact from place to place, just as the incidence of duodenal ulcer does. A. F. Hurst and M. J. Stewart[4] found that 12% of gastric ulcers coming to post mortem were associated with a duodenal ulcer. D. P. D. Wilkie[5] estimated that 50% of gastric ulcers coming to operation were associated with a duodenal ulcer. In 25% of Johnson's[6] cases of gastric ulcer there was an (antecedent) duodenal ulcer present as well. From our own series of 1,015 gastric ulcers[7] we excluded 145 (13%) of combined or pre-pyloric ulcers.

Clarke and his co-workers do not mention whether in the figures they give they exclude combined ulcers from the gastric ulcer series as they did in an earlier paper.[8] In the paper[7] in which we first showed the association between group O and duodenal ulcer, the series of gastric ulcers which we also analysed did not include combined or pre-pyloric ulcers, so that the O predominance in these groups does not explain wholly the geographical differences that have emerged in the relationship between gastric ulcer and group O, though a difference in applying the term "juxta-pyloric" might be important in this respect.

In Johnson's[3] series of 523 gastric ulcers, strictly selected type I gastric ulcers gave a group O percentage of 44.9, combined ulcers a group O percentage of 54.8, and pre-pyloric ulcers a group O percentage of 60.2 against a control group O percentage of 45.8: these differences are just significant at the $P<0.05$ level.

In this type of work we cannot be too frequently reminded that a new fact, and particularly an unexpected fact, emerging from statistical analysis requires support from much higher levels of significance than the conventional. This reminder is particularly necessary when statistical analysis is applied to many different comparisons within a single collection of numerical data. The figures which Clarke and his team have presented are nevertheless a clear encouragement for the collection of greater numbers.—I am, etc.,

Postgraduate Medical School, London, W.12. IAN AIRD.

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Long-term Anticoagulant Therapy

SIR,—The findings of the Medical Research Council's trial on long-term anticoagulant therapy (*Journal*, March 28, p. 803), according to which the recurrence rate of myocardial infarction is reduced to one-fifth, coupled with all previous favourable reports, will inevitably lead to a greatly increased use of this treatment. I would like, therefore, to stress the dangers of an all too frequent present-day practice. Patients on long-term anticoagulants admitted to hospital often have their anticoagulant therapy stopped for no apparent good reason. In my experience, in the vast majority of patients with *severe, advanced* ischaemic heart disease, when long-term anticoagulant therapy has been stopped, the patient has died shortly afterwards. It is unnecessary to stop (as opposed to adjust) anticoagulant therapy in any patient except when haemorrhage has occurred accompanied by a low prothrombin level. This applies even where the need for major surgical intervention arises, or in the presence of intercurrent infections.

One further point needs emphasizing, and that is the necessity for adequate anticoagulant control. Of 176 patients of mine on long-term anticoagulant treatment for six months and over, 149 were considered to have adequate anticoagulant cover. The total mortality and recurrence rate of further myocardial infarction in this group was only 10.7%. However, in the remaining 27 patients, who were considered to have inadequate treatment, the total mortality and recurrence rate of myocardial infarction was 44%. These figures speak for themselves. Inadequate control means in fact "no treatment," with the added risks of haemorrhage. To carry out consistently adequate anticoagulant treatment for an indefinite period of many years or more calls for the provision of special anticoagulant clinics where individual attention can be given to every patient by experienced clinical and pathological personnel. I would make an analogy with the benefits of treating severe diabetics in a well-run diabetic clinic.—I am, etc.,

New End Hospital, London, N.W.3. M. TOOHEY.

Reappraisal of Thymectomy

SIR,—Our purpose in writing this letter is to express the hope that those who wish for guidance on the treatment of myasthenia gravis will not remain confused after reading Dr. H. Windsley's attempts (*Journal*, March 14, p. 717) to simplify a complex problem. Little help in the choice of treatment can be expected from a comparison of the two lists he provides of percentage results calculated by different methods. The excellent monograph on myasthenia gravis recently published by Dr. Kermit E. Osserman,[1] however, provides a critical assessment of the results of thymectomy reported by different observers, of whom Sir Geoffrey Keynes is by far the most experienced. Dr. Windsley's statement that "until recently the thinking about the natural history of this disease or syndrome has been rather uncertain" may suggest to some that a greater measure of certainty has now been reached, a conclusion which, alas, is not supported by any convincing evidence. Nevertheless the desire to do so can be implied from the number and variety of papers to be discussed at the forthcoming Second International Symposium on Myasthenia Gravis to be held in Los Angeles in April. The account of this, which is to be published in 1960, may serve to emphasize, as did the First International Symposium held in 1954, the merit and wisdom of those who reflect and give expression to second and subsequent thoughts on the fascinating and challenging problems of this disease.—We are, etc.,

Liverpool. GEORGE W. PENNINGTON. ANDREW WILSON.

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Rubella in Pregnancy

SIR,—Dr. Julia Bell, I am sure, is going to be very angry with me for having very sincere doubts about accepting her answer to the problem of rubella in pregnancy (*Journal*, March 14, p. 686)—a Herod-like slaughter of all children whether they are affected or not. The method of collecting her 712 cases she criticizes herself with some vigour, so that she does not suggest that the 421 affected cases give a hint of the real chance of an affected child. Perhaps, as she suggests, Professor Bradford Hill will produce a figure to guide us, but I am sure he will not issue an edict on this difficult problem. The final decision to terminate a pregnancy or not must be made by the obstetrician who carries out the operation, which all agree is the most distasteful operation one may be asked to perform and depressing not only to the operator but also to the patient herself.

What is a practitioner to do when one of his patients develops rubella in pregnancy? I suggest that before giving an opinion he should arrange as a matter of urgency a conference with his colleagues in obstetric practice at the patient's home or at the surgery with necessary time and privacy. Certain facts can then be established, such as the certainty and severity of the rubella and the size of the uterus as estimated by dates and bimanual examination. Finally, before any discussion with the patient the religious convictions of both parents must be ascertained. After discussion between the obstetrician and the practitioner the patient and her husband can be interviewed to hear a unanimous opinion or on occasion opinions in disagreement. It is important to underline that we are offering an opinion, and we should assume that the patient and her husband have already had advice from the loudspeaker or television screen. For example, I have had the experience of advising against termination for rubella to have the parents tell me Professor X, well known on the radio, knew better—he advised routine termination *actually over the radio*, and what had I to say to that . . . ? There is no answer, of course. One gives an opinion and retires, making it easy for the patient to seek further advice without delay, perhaps at some centre nearer to Broadcasting House.

All this difficulty and divergence of views make it very difficult for the patient, who would naturally prefer us to be unanimous, but I must emphasize that in our part of the world obstetric (Protestant) medical opinion varies widely on the problem of rubella in pregnancy from agreement with Dr. Bell to strong disagreement. Moreover, in the numerous discussions I have had with colleagues on the problem of the foetus and child-at-risk the question has often been posed: Are we to be asked to terminate if the foetus is at risk from the virus of infective hepatitis or pneumonia or (overseas) from untreated malaria or even attempted abortion, whether by instrument or noxious drug? All put the baby at risk, but where shall we finally draw the line?

On the more constructive and certain ground of prophylaxis, the protection given by an attack of rubella in childhood underlines the need for propaganda by press and radio to share our German measles with other families. I was surprised recently to discover that the idea was new to the headmistress of a school for girls with whom I had some recent correspondence. From an obstetrician's viewpoint it is much more important to make sure that his daughter has rubella than to pass the "11 plus."

In the important matter of protecting pregnant mothers perhaps the press and radio might agree to use a headline "Mothers-to-be run from German measles." It is, of course, quite a family upset to leave one's home and district to avoid the risk of contact with a boy or girl from a "rubella class" at school, or to avoid contact with one's own child, but contrast this with the agony of doubt and anxiety if rubella should complicate early pregnancy.

Finally, even if a pregnancy is terminated at the request of the parents and her doctor (and I am not suggesting for a moment that I personally should agree to do so, as a matter of routine), it is important to realize that the emptying of a uterus, itself an operation not without risk and certainly not without much mental anguish for the parents, is a feeble answer to a very difficult problem, and, furthermore, the chance of removing a perfectly normal child is perhaps as high as 8 or 9 out of 10.

Perhaps Dr. Julia Bell will recognize a lack of fierce logic in my approach to terminating pregnancy: if so she is quite right, for I admit to some emotional bias. My oldest daughter, now in her first year at the university, was about 4 weeks in utero when her mother had a fierce attack of rubella. If Dr. Julia Bell had been around in 1939, who knows, my daughter might not be here to read her article and ask, "Daddy, whatever does Dr. Bell mean by *treatment*? Does she mean she would have removed me . . . just in case?"—I am, etc.,

Birmingham, 15. H. C. MCLAREN.

Abortion on T.V.

SIR,—I can certainly endorse your editorial comment (*Journal*, March 7, p. 638) that the gynaecologist's account of the complications of therapeutic abortion cannot have been very comforting for those about to undergo it. One patient under my care, who had been advised to consider undergoing this procedure because of a grave medical disorder, saw this programme and concluded that the risk of having a therapeutic abortion was at least as great as that of proceeding with the pregnancy in all circumstances. I did not see the programme myself, so I cannot say whether this was a just conclusion; I can say that it took some time to restore the patient's confidence in her medical advisers and that I was unable to answer the patient's indignant query: "Why do they say these things on television if they are not true?"—I am, etc.,

London, W.C.1. R. A. GAWN.

When to Tie the Cord

SIR,—I was most interested to read the article by Dr. R. J. K. Brown (*Journal*, February 14, p. 404) and the subsequent letter of Dr. W. N. Leak (*Journal*, February 28, p. 584) highlighting the uncertainty as to when to tie the umbilical cord after birth. This problem is also of considerable importance in veterinary medicine, and I wonder if I might contribute some information on the comparative aspects of parturition in the domestic animals.

In the thoroughbred mare we have observed[1] that the great majority of parturitions take place when the mare is recumbent, and the cord naturally remains intact for up to 20 minutes until ruptured either by the mare rising to her feet or by the struggles of the foal. During some of this time, often for as long as five minutes, pulsation is readily detectable in the umbilical arteries, and if the cord is severed immediately after delivery up to one and a half litres of blood—i.e., at least 25% of the potential blood volume of the foal—may be obtained from the cut maternal end. On the other hand, if the cord is left until after pulsation has ceased it is difficult to collect even 200 ml.

It has been the common practice in thoroughbred studs in this country to bring mares into loose boxes to foal, and to sever the cord immediately after delivery.

It may be significant that under such conditions of husbandry a syndrome is sometimes seen in the newborn foal which bears some striking similarities to the pulmonary syndrome in infants.[2] On the other hand, this syndrome has never been recorded under more natural conditions where mares foal unattended and outdoors.[3] It is tempting to conclude that the condition in foals therefore arises as a result of man's interference, as has been suggested by Dr. Brown with regard to the appearance of pulmonary hyaline membrane in infants.

In contrast to the human and the horse, severance of the cord frequently occurs during the second stage of labour in the sheep and the ox owing to the relatively short length of the cord. Barcroft[4] estimated that the amount of blood transferred from the placenta to the lamb was in the order of 80 ml. In this case it would seem probable that any transfer that occurs must do so before delivery of the foetus is complete.

Among the species normally bearing a single foetus the human and the horse appear to be the only ones where, in a normal delivery, interference of the cord is carried out as a routine, and the transfer of placental blood artificially prevented.—I am, etc.,

Newmarket. PETER D. ROSSDALE.

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4 Barcroft, J., *Lancet*, 1941, **2**, 91.

Anaesthesia in Domiciliary Midwifery

SIR,—Mr. S. Bender is to be congratulated on his excellent review of the obstetric problems of the general practitioner (*Journal*, February 21, p. 497). I must, however, take issue with him over his advocacy of chloroform anaesthesia for manual removal of the placenta. In giving some contraindications to its use, Mr. Bender admits some of its risks, and I think that few will deny the supreme safety of open ether. The risk of giving open ether in a room with a fire is slight provided one doesn't smash the bottle, and manufacturers in this country might help in this direction by making it available in tins or plastic containers. The way to avoid all risk from a fire, however, is not to give chloroform, but to put the fire out. It is not usually as difficult as it sounds to remove the ashes with a shovel, though sometimes, as with the old-fashioned grate with bars or some of the modern all-night burners, there is more trouble, but, if the worst comes to the worst, the rather more messy method of pouring water on the fire from a kettle can be adopted. The subsequent relighting of the fire provides useful occupation for worried relatives.

If, however, Mr. Bender means that "rag-and-bottle" anaesthesia should be still taught to students and new graduates, I couldn't agree more, but it looks as if this will have to be done by obstetricians and general practitioners, as a new generation of anaesthetic specialists and teachers is now growing up which looks upon both ether and chloroform as being of historical interest. In these days, when the complications of obstetrical anaesthesia are so much in the news, it should be kept in mind that rag-and-bottle methods are almost completely devoid of the risk of inhalation of vomit which now hangs like a black cloud over other methods. Ether has now been in use for just over a century, and procaine for over half a century, and I venture to suggest that they will still be in use after newer drugs and techniques have been forgotten. Indeed, I would claim that anyone who confines his anaesthetic practice in obstetrics to the use of open ether, or 0.5% procaine, will remain free from fear of having an anaesthetic fatality.—I am, etc.,

Middlesbrough. BRYAN WILLIAMS.

Glucose

SIR,—The recent recommendations of the Foods Standards Committee[1] are, on the whole, to be welcomed as bringing soft drinks into line with other foods, which have standards set in order that the public can expect value for money. However, I was sorry to find that the use of sugar in one form or another was to be made compulsory in place of saccharin. The quantity of soft drinks imbibed by some children accounts for quite a large number of calories. If the child is eating a reasonable diet, these calories are in excess of requirements and from the medical point of view the sugar does no good, any more than saccharin would. If the child is eating a poorly balanced diet, the sugar simply adds to the existing predominance of carbohydrate in the diet, and spoils his appetite.

In the school health service we have now had to turn our attention from the child who is underweight and underfed to the fat child who is eating too many calories.' We cannot stop this fat child slaking his thirst with soft drinks, but at least we can see that they do him no harm by insisting that saccharin is used in their manufacture rather than sugar. Drinks for the child who is unwell is quite another matter, and, although one soft-drink manufacturer is making the medical and nursing professions sick of his pseudo-medical advertisements, there is no objection to the use of sucrose or glucose in drinks intended for sick children and advertised as such.—I am, etc.,

Middlesbrough, Yorks. W. J. WIGFIELD.

REFERENCE

1 Food Standards Committee of the Ministry of Agriculture, Fisheries, and Food, *Report on Soft Drinks*, 1959. H.M.S.O.

SIR,—I read with interest Dr. A. H. Douthwaite's letter in the *Journal* of March 7 (p. 646). As a general practitioner, I have found drinks which contain glucose to be an admirable method of providing "calories" in palatable form, particularly for sick children and patients suffering from gastric upset.

I think it is imperative that the profession should be free to exercise their own discretion in assessing the clinical value of glucose as an adjunct to therapy. It seems to me that sucrose, in view of its sweetness, would be a useless substance to administer to an easily nauseated patient or convalescent.—I am, etc.,

London, N.21. J. H. EDGAR.

Dirty Food

SIR,—Dr. W. A. Bowdler, in his letter on the above subject (*Journal*, March 14, p. 719), draws attention to a very important problem, but it is felt that it should be pointed out that the Council of the Royal Institute of Public Health and Hygiene has for a long time been greatly concerned with the need for more proper food inspection and handling in restaurants, eating-houses, and, in fact, in the training of staff in any way connected with the handling and preparation of food. In this connexion we would draw your attention to the courses which are organized under the auspices of the Institute in various centres all over the country leading to an

examination in "food hygiene and the handling of food." Some of these courses are on a part-time and others on a full-time basis and the lectures are given mainly by members of the medical profession.

The Institute therefore welcomes such letters as Dr. Bowdler's which so clearly draw attention to the present lack of hygiene displayed in many cases, and inquiries concerning the aforesaid courses and examination would be given every attention if addressed to the Secretary of the Institute at 28, Portland Place, London, W.1.—I am, etc.,

London, W.1. J. C. AINSWORTH-DAVIS,
Chairman, Executive Council,
Royal Institute of Public Health and Hygiene.

Mental Health Bill

SIR,—Under this Bill it seems possible that there may be an opportunity of reorganizing the administrative arrangements in mental hospitals to allow individual consultant psychiatrists full responsibility for their patients, on a basis similar to that already established in general hospitals. This will mean a modification of the present mental hospital medical superintendent system; although it does not necessarily follow that superintendents will lose in status in any revised arrangement.

There are clearly many factors of major clinical significance involved in such a change, and they probably apply to psychiatric work in general hospitals as well as in the mental hospitals. We feel that consultant psychiatrists who are not medical superintendents may welcome opportunities of discussing these factors, and perhaps formulating views which may be put forward more effectively if they represent the results of considered group discussion rather than the views of single individuals.

We should like therefore to invite senior clinical colleagues in this category who are interested in taking these questions further to send their names to one of the undersigned. Depending on the results of this invitation we should undertake to try to arrange for occasional discussions on a tentative basis, and if it seemed helpful to report any conclusions reached.—We are, etc.,

Taunton. M. F. BETHELL.
Hornchurch. R. W. CROCKET.
Oxford. JOHN E. DUFFIELD.
London, S.E.5. A. HARRIS.
Ipswich. J. G. HOWELLS.
Coulsdon. JOHN T. HUTCHINSON.
Warwick. C. TETLOW.
Sutton. A. S. THORLEY.

Hypnosis for Patients with Burns

SIR,—Having read about the difficulties Drs. B. L. Finer and B. O. Nylén encountered when giving repeated anaesthetics to a patient with third-degree burns (*Journal*, March 7, p. 624), I cannot help wondering whether the use of hypnosis was ever given consideration.

Such a patient, anxious and dreading repeated anaesthetics, is very often the one who welcomes and therefore responds well to the use of hypnotic analgesia, and if he is found to be a suitable subject he rapidly loses his fears and becomes calm and co-operative.

The advantages of using hypnosis are many. These include the avoidance of the use of large doses of depressant drugs and also the periods of starvation before and after each anaesthetic. Furthermore, the analgesia can also be extended into the post-operative period.

Although in no way advocating hypnosis as a routine, I suggest that its possibilities should always be considered when planning anaesthesia for the problem case.—I am, etc.,

Hitchin, Herts. O. H. E. BAYLES.

Bromism and "Relaxa-tabs"

SIR,—Concern has been recently expressed about the possible harmful effects of sleeping tablets containing open-chain ureides, some of which contain bromine. Many of these are available to the public without prescription. One such preparation is "relaxa-tabs," consisting of carbromal, bromvaletone, and calcium phosphate, containing bromine equivalent to approximately 2½ gr. (143 mg.) of potassium bromide in each tablet. The danger of bromism from this preparation is well illustrated by the following case.

A young man of 26 was brought by a friend who was concerned by the patient's recent outbreaks of physical violence, irritability, depression, and insomnia, together with a change in personality which he found difficult to put into words.

The patient had started taking relaxa-tabs three years previously. Over the last six months he has been taking about eight tablets to get himself started in the morning, and a further eight tablets to calm his tension later in the day. The patient complained of being depressed and of being unable to control his feelings of violence when upset by others, which was happening with decreasing provocation and increasing frequency. He interpreted the physical restraint applied at these times as active persecution. He also complained of loss of libido for seven months, early morning waking, decreased fluid intake, variable appetite, and intermittent constipation.

On examination he was tense, and there was a long-standing atrophy of both testicles. His eyes were slightly bloodshot with fixed dilated pupils, and the mucous membrane of the mouth was bright red.

After consultation it was thought that some of the symptoms could be due to bromism. The serum bromide was found to be 197 mg. per 100 ml. (toxic level 100–200 mg. per 100 ml.). He was therefore instructed to discontinue the relaxa-tabs, to increase his dietary salt to the limit of toleration, to increase fluid intake, especially tea and coffee for diuretic effects, and given a regular aperient. (The more active procedures for expediting bromide excretion were felt not to be indicated because of the bromide level and the probable refusal of the patient to co-operate.)

The relaxa-tabs were effectively replaced by chlorpromazine with barbiturates. There was symptomatic improvement over the ensuing period. The serum bromide fell to 115 mg. per 100 ml. after ten days, and then to 54 mg. per 100 ml. after a further fourteen days, and to 26 mg. per 100 ml. after a further two weeks.

Whilst carbromal may itself be toxic we have here assumed the symptoms were due to bromism.—We are, etc.,

London, W.1. F. O'DONNELL FINIGAN.
London, S.W.1. M. A. KALINA.

Treatment of Measles

SIR,—Your annotation (*Journal*, January 24, p. 223) and the subsequent letter by Dr. Drummond Ellis (February 14, p. 435) recall an incident worth recording.

Some three years ago an outbreak of measles commenced in a hospital for coloured tuberculous

children. It began in a male block containing 50 beds, and within a fortnight there had been 13 deaths. At the height of the epidemic I was able to obtain 50 ml. of gamma-globulin and gave each of the 50 patients in the female block 1 ml., varying the dose but slightly according to age, as my margin was limited. Within a few days measles broke out in these wards, but the incidence was 50% less and I had no fatalities. The product used is manufactured by the South African Institute for Medical Research from pooled donors and is said to contain antibodies in 10-fold concentration.—I am, etc.,

Port Elizabeth, South Africa. P. JABKOVITZ.

Surgical Rehabilitation of Delinquents

SIR,—May I encroach a little on to your available space to answer some points which have arisen concerning my article (*Journal*, February 14, p. 432)? Dr. G. M. Carstairs (*Journal*, March 7, p. 650) asks for some comparative figures for numbers of "untreated cases." The position is that the number of inmates discharged from a Borstal institution varies from month to month and year to year, so that it is possible to give only an average figure to cover the period of the project, and this would work out at about four "untreated" cases for each case the subject of remedial surgery. Dr. A. A. Bartholomew (*Journal*, March 7, p. 650) raises doubts that the case is proven in the courts of methodology, and I fully accept his right to regard the matter in that light, but to satisfy methodology completely it would have been necessary to find a group of delinquents with the same disabilities, coming from identical social backgrounds and of the same degree of criminal sophistication. Half of the group should then have been given the benefit of surgical rehabilitation and the other half retained as a control. I hope Dr. Bartholomew will agree that this would be impossible, quite apart from the ethical question of holding back treatment which, as a doctor, one should advise.

However, was the project, as carried out, quite so far from ideal as is suggested? First, at a Borstal institution the selection of inmates is not random. A very careful screening at allocation centres causes the population at a given institution to be of similar age, social background, and criminal sophistication, and this is particularly true of the institution where the project was conceived. Secondly, it is true that the surgical rehabilitation cases received supportive minor psychotherapy—and it is precisely for that reason that my conclusion is that it is the combined picture which must be regarded. Furthermore, all inmates at the institution receive special individual attention, so that the difference is that the surgical group received one particular attention and not the only particular attention available. The conclusion I draw is that this particular attention proved the most valuable.

I agree with Dr. Bartholomew that it is important to restrain claims which cannot be absolutely proved, but methodology can be carried to such extremes that it is virtually impossible to satisfy the conditions required, especially working at a delinquent institution. When the difference between the treated and untreated cases is considered, statistical analysis suggests that the difference falls outside the realms of chance—but direct comparison of the results achieved in each surgical section is not warranted. My conclusion that remedial surgery renders the individual susceptible to the normal character training processes is not "drawn from inadequate work that lacks the necessary degree of methodological sophistication," as Dr. Bartholomew suggests: it is a direct observation. These youths *did* prove more amenable and more ready to listen on return from surgery, and nursing staffs invariably commented on the change.

I do not suggest that the figures I quoted in my article would be exactly reproduced if the project could be repeated, but Dr. Bartholomew himself confirms that my conclusions are supported by his own experiences and mentions that Sir Harold Gillies has recorded experiences in plastic surgery which accord. I remain convinced that there is a crying need for further development of the use of remedial surgery in delinquency, and believe the best proof of the pudding will lie in the further eating thereof.—I am, etc.,

H.M. Prison, Wakefield, Yorks. D. A. OGDEN.

Refusal of Parental Consent to Treatment

SIR,—The N.S.P.C.C. has had this matter under consideration for some time past, and my attention has been drawn to the article by your legal correspondent under the heading "Conscientious Objection to Transfusion" (*Journal*, January 10, p. 120). I am in agreement with his opinion that, where parents refuse consent to their child receiving necessary medical treatment, a doctor would be justified in placing the facts before the N.S.P.C.C. It is questionable, however, whether in such circumstances the Guardianship of Infants Acts (which deal mainly with questions of custody as between parents) are the legal machinery with which to secure the urgent needs of the child.

The law upon this subject is briefly as follows. Under the Children and Young Persons Act, 1933, a parent is guilty of the criminal offence of wilful neglect in a manner likely to cause unnecessary suffering or injury to health if such parent fails to provide adequate medical aid for a child under 16 years of age. The refusal of a parent to consent to medical treatment of the child on the ground of religion or any particular form of belief is of itself no defence. An application can also be made to the juvenile court in respect of a child who is in need of care or protection, including the case where the parent is guilty of neglect of the child. The juvenile court has power to commit the child to a "fit person," and such person then has the same rights and powers and is subject to the same liabilities as if he were the child's parent. The Act also gives power to a magistrate to order the immediate removal of a child to a "place of safety" until the child comes before the juvenile court. This is an important power, since the child can be kept in a place of safety while any prosecution against the parent for neglect and any application to the juvenile court to commit the child to a fit person is being dealt with. "Place of safety" is defined as "any home provided by a local authority, any remand home, or police station, or any hospital surgery, or any other suitable place the occupier of which is willing temporarily to receive him."

Over a period of some 75 years the N.S.P.C.C. has dealt with a number of cases where a parent has refused, without good cause, to give consent to medical treatment which was required to prevent unnecessary suffering or injury to health. In such cases a removal order was obtained and the parent prosecuted for wilful neglect. After the conviction of the parent application was made to the juvenile court for an order for the child to be committed to the care of a fit person, and after such order had been made the fit person gave the consent to the medical treatment. All this takes time, and some of the new treatments must be carried out within a very short period, as in the case of a blood transfusion. Some time ago the N.S.P.C.C. obtained counsel's opinion as to the action which should be taken in these cases of emergency. Counsel advised that the proper procedure is to apply to the magistrate for an order for the removal of the child to a place of safety under the

Act, and, on the child being removed to a place of safety, the occupier of the place of safety has, in counsel's view, the same power to give consent to the medical treatment as a "fit person," although this is not expressly mentioned in the Act.

Thus where a child is in need of immediate medical treatment, and there is the necessary medical and other evidence concerning the parent's refusal, the removal of the child to a place of safety can be effected upon information laid before a magistrate, and it would then be for the occupier of the place of safety to give the required consent. Fortunately a case of this type seldom arises, but the N.S.P.C.C. would deal with each case on its merits immediately it was reported. The medical evidence required would be (1) that the doctor had explained fully to the parents the condition of the child and the urgency of the treatment required and had warned the parents of the harmful effect upon the child of any delay in treatment; (2) that the doctor was of the opinion that refusal to consent to the treatment being given without delay was likely to cause unnecessary suffering or injury to the health of the child; and (3) that the risks (if any) involved in the treatment would not justify the parents in refusing to give consent—i.e., the parents had no reasonable grounds for withholding their consent.

It will be seen that without the assistance of doctors the N.S.P.C.C. is in difficulty in trying to help children in these circumstances, and I do hope you will feel able to publish this letter so that your readers may know how the N.S.P.C.C. deals with these cases.—I am, etc.,

London, W.C.2.

ARTHUR MORTON,
Director,
National Society for the
Prevention of Cruelty to Children.

Immunization Programmes

SIR,—We have been greatly interested in the discussions you have just published on the "calendar" of vaccinations. You may perhaps think fit to inform your readers of our present position on this subject.

We do not advise smallpox vaccination (nor, generally speaking, any other vaccination) in the first month of life, except if circumstances suggest that the child might subsequently be reared away from any medical centre (which is unlikely in France or the United Kingdom). We give priority to pertussis immunization: we advise to have it performed if possible in the course of the second, third, and fourth months. Should it be associated with diphtheria and tetanus inoculations? We believe that it should. The results obtained in France, as in Great Britain and elsewhere, are encouraging and there is no other means of reducing—as would be desirable—the total number of injections to be made. Smallpox vaccination should take place in the fifth month.

Poliomyelitis immunization has so far been tried in combination with others in a limited number of cases. When the results of these trials are known, we may be able to recommend it in association. For the time being it seems to us preferable to perform poliomyelitis inoculations separately. As a rule we give the first shot in the sixth month. In this way, if the interval between the injections does not exceed one month, the third injection is given at the age of 8 months. Thus, if for one reason or another the schedule of the operations is delayed, it is still possible to have all the inoculations completed before the age of 1 year. We remain faithful to the booster one year after the combined diphtheria and tetanus vaccination. The same applies no doubt to poliomyelitis immunization. As regards B.C.G., we think that in a non-contaminated environment it is not necessary to perform it before the third year of life.

Finally, we should like to stress the absolute need for periodical revaccinations, not only against smallpox but also against diphtheria and tetanus. As regards tetanus prophylaxis, an injection of anatoxin (toxoid) every six to eight years at the most is certainly indispensable. It goes without saying that all these indications apply only in an epidemiological situation similar to that prevailing in France to which that of Great Britain is roughly comparable. It is understood, too, that this calendar may have to be modified in relation to advances that may be made in the preparation of vaccines, and to further studies of the infants' response to these various inoculations and to their timing.—We are, etc.,

International Children's Centre,
Paris, 16.

ROBERT DEBRÉ.
F.-M. LÉVY.

Invalid Vaccination Certificates

SIR,—Dr. I. J. Corbett's letter (*Journal*, March 7, p. 644) is timely in raising the whole question of the present method of stamping vaccination certificates. I do not know how the present system operates in the provinces or whether the patient who is vaccinated in his or her home often has to travel far for the official "approved stamp." I only know that in central London the present system is quite ludicrous, and in my experience the stamp is absolutely meaningless. In the busy London casualty departments many vaccinations are carried out by a constantly changing medical staff. Do the local authority health departments have the signatures of this staff so that they can be authenticated as the stamp requires? I am quite sure that they do not, any more than they have the signatures of any local practitioners in a given area.

In the past few weeks I have deliberately taken along patients' certificates (usually supplied by me) to the local authorities myself for stamping. I was not known in the offices of five authorities I visited, nor so far as I am aware have they ever had my signature. In nearly every case the card was stamped "Doctor's signature authenticated" without any question. It was quite clear to me that there was no question of anyone authenticating my signature; stamping the card was almost automatic. On one occasion I was asked where the doctor practised, and upon my saying Chelsea the card was stamped.

In Westminster, where I took one card, I was asked where the doctor practised and revealed that I was the doctor. In spite of my offering to produce my identity card, driving licence, and a visiting card, and to write my signature so that the one on it could be authenticated, I was told that this could only be done in Chelsea. Yet on other occasions other authorities stamped cards for vaccinations performed in Chelsea without any questions whatever. This matter was first brought to my attention by one of my patients who, without my knowledge, having had to travel across London some distance to get his card stamped in my area, on a later occasion took in a card with a mythical name on it, forged my signature, and had it stamped without any question. He then sent the card to me with suitable comments on the medical procedure which allowed such stupidity.

Surely the answer to this problem is simply for the Ministry to issue on demand to hospitals, general practitioners, and other doctors who carry out vaccinations suitably stamped cards which do not require the present useless stamping by clerks who will not and cannot "authenticate the doctor's signature." This might cut down staff in the local authority's health department, save many patients a great deal of time, enable last-minute travellers to avoid much unnecessary anxiety, and cut out what seems to be dead and unnecessary red-tapeworm.—I am, etc.,

London, S.W.3.

NOEL H. MOYNIHAN.

Treatment of Migraine

SIR,—Dr. Raymond Greene's articles (*Journal*, February 28, p. 574; March 7, p. 639) on the drug treatment of migraine are most comprehensive and informative, but may I venture to ask if we are wise to contemplate the treatment of this trouble without bearing in mind the fact that in quite a proportion of cases refractive errors of the eyes can play a part in causation and their remedy can cure? An old friend and fellow-student of my own on reaching middle life developed severe migraine, sometimes dropping unconscious in trains on the underground railway and having to be lifted out and left on the platform of the next station until he recovered. After various glasses had been prescribed without benefit, a fresh oculist hit the bull's eye with a correction and he had no further migraine.—I am, etc.,

Southsea. M. ASTON KEY.

Influenza Epidemic

SIR,—Like Dr. J. Hume Stewart (*Journal*, March 7, p. 645) I also have seen these pyrexial children, usually influenza contacts, and they too have had scattered moist sounds in one or both lungs, which, misguidedly perhaps, I did not interpret as pneumonia. So far they have all cleared rapidly with mist. acid. acetylsalicyl. pro inf.—I am, etc.,

Chelmsford, Essex. E. M. HUME.

British Association of the Hard of Hearing

SIR,—As president of the British Association of the Hard of Hearing, may I draw the attention of your readers to the excellent help that it is able to give to patients who suffer from a chronic impairment of hearing that is found not to be amenable to medical or surgical treatment?

The clubs, at which new members are warmly welcomed, are provided by different branches of the association. Social evenings are regularly held. There are classes for deafened adults to help them to acquire skill in using hearing-aids and in lip reading. Frequently there is a youth section for young men and women who have not been able to find opportunities for enough social life elsewhere.

My wife and I, through long experience in the University of Manchester of holding evening classes and informal meetings for adults who have suffered a partial or total loss of hearing, know how much help can be given to them both occupationally and socially. The clubs help these people to learn to live with their deafness. Persons suffering from a total loss of hearing are always sure of an understanding welcome in the clubs of the association. It has been noted, and we have observed it to be true, that a progressive loss of hearing in later middle age is liable to be a source of much unhappiness and mental stress.

The resources of the British Association of the Hard of Hearing, its offices, and members are available to help all people for whom loneliness and anxiety have become a consequence of deafness. The hon. secretary, Mr. C. H. Mardell (The British Association of the Hard of Hearing, Briarfield, Syke Ings, Iver, Buckinghamshire), will be glad to send to anyone who is interested the address of the nearest branch of the association.—I am, etc.,

Department of Education of the Deaf, University of Manchester. A. W. G. EWING.

Obituary

T. MURRAY NEWTON, M.B., Ch.B., F.R.F.P.S.

Mr. Murray Newton, honorary consulting surgeon to the Western Infirmary, Glasgow, died on March 19 at the age of 68.

Thomas Murray Newton was born on October 21, 1890, and studied medicine at Glasgow University, graduating M.B., Ch.B. in 1913. During the first world war he served with the R.A.M.C. in France and Mesopotamia, and his future career was probably determined by an association at that period with a young surgeon who was later to become, as Sir John Fraser, professor of clinical surgery and principal of the University of Edinburgh. Newton returned, however, to general practice for a few years in Grimsby, where he was honorary secretary of the old North Lincoln Division of the British Medical Association in 1923–4, and later in Glasgow, an experience which he cherished and which remained throughout his life as the broad background against which he practised his specialty. Not until 1925 did he see his way to devote himself to surgery. He then joined the staff of the Western Infirmary undismayed by the seniority of some who were his juniors in age. He became a Fellow of the Royal Faculty of Physicians and Surgeons in 1925, and soon developed a special interest in the surgery of the thyroid gland. In this he was to become a master. Those were times when diagnostic aids in this field were by present standards primitive, and when assessment by clinical observation and experience was all-important. In this he excelled, and many surgeons who visited the Western will recall the modest authority with which he would discuss a problem and the confident dexterity with which he operated. Both in the Western Infirmary and in the Dumbarton Hospital he continued to practise a wide variety of general surgery, but the thyroid was his love. When the B.M.A. held its Annual Meeting at Glasgow in 1954 he served as a vice-president of the Section of Surgery. He retired in 1956.

A. B. K. writes: If all surgeons in charge of wards were Newtons the hierarchical system would be universally adopted. He had a capacity to see the virtues of even the weakest; he sought no glory; his greatest pride was in the achievements of his juniors. To them and to students he taught the treatment of the patient as an individual. Perhaps he liked to be regarded as something of a sceptic, but he was not unreceptive of new ideas. There was one abiding test to which he subjected his decisions, "Is it in the interests of this patient?" His broad humanity and patent sincerity made him confessor and counsellor to a multitude of younger men. The stories which he delighted to tell had only one victim—himself. To those who knew him it was no surprise that he became the first chairman of the Central Consultants and Specialists Committee in Scotland. The profession could not have had a better guide in those formative years of the National Health Service. He was sustained through many a trial by a deep faith in God and humanity. His days of relaxation were memorable if they could be spent with friends or family on a Highland loch or river with rod and line. He is survived by his widow, two medical sons, and two daughters.

R. B. W. writes: With the passing of Mr. T. Murray Newton the West of Scotland has lost a fine surgeon and an admired and respected man. Murray Newton was much more than a consultant surgeon—he was regarded as a father confessor by his colleagues, junior and senior, surgical and medical. All brought their problems, clinical, professional, even social and domestic, to him knowing they would receive a patient hearing, a sane appraisal, and all the forthright advice and assistance that he could give. Essentially conservative in attitude and outlook, "T.M.N." was a neat and skilful surgeon, but could be bold and radical when the occasion demanded. He made a special study of the surgery

of goitre and was a pioneer in Scotland of the Böhler techniques of fracture treatment. Although he did not contribute to surgical literature he was an ardent student of it. His teaching of undergraduate students was sound, and aimed at inculcating the principles of proper professional conduct and producing graduates who would make good doctors. He clung to the highest ideals, professional and ethical, and his integrity and high sense of duty won him the respect and affection of all. His handling of patients, relatives, tissues, and examinees all bore the stamp of the true surgeon—gentle, deft, firm.

T.M.N. was a champion of the younger men in the profession, especially those whose careers had been interrupted by war service. At the inception of the National Health Service he strove energetically on many committees to ensure that professional standards and rights were not impaired. No lover of bureaucracy, and passionately opposed to a whole-time salaried service, he did more than most to ensure that the great experiment of the National Health Service got off to a fair start.

But it will be as a man that T.M.N. will be remembered, a man of four loves—justice, his profession, his family, and fishing. Any cause, great or small, if it was a just one, had his unstinted and energetic support. Only those privileged to work close to him realized how heavily he leaned on his devoted life partner, Janie, whose loving care and affection sustained him through the many ordeals and setbacks of the last ten years. Fishing was his hobby and relaxation. To see the impish glint in his eyes on a forenoon when he had arranged to play truant and go for an afternoon's fishing was an unforgettable insight into the essential goodness and humanity of this beloved man.

R. L. KITCHING, M.B., B.S.

Dr. R. L. Kitching, who was in general practice at Wetherby, Yorkshire, for 40 years, died at his home there on March 16. He was 69 years of age.

Robert Lacy Kitching was born at Scarborough on May 6, 1889, and was educated at Oundle, Cambridge University, and St. Bartholomew's Hospital. He graduated M.B., B.S. from Durham University in 1913, and then held the appointments of ophthalmic house-surgeon and house-physician to Sir Wilmot Herringham at St. Bartholomew's Hospital. Before graduation he was captain of Bart's rugby fifteen in the same season as his twin brother was captain of the Cambridge fifteen. Later he played for Blackheath and Middlesex, but all that stopped in 1914, when he went to France as a regimental medical officer in the King's Own Yorkshire Light Infantry. In 1916 he came home seriously ill, but went out again early in 1918 only to fall a victim to the influenza epidemic of that year, which put an end to his service overseas. In 1916 he married Alyson, the daughter of the Rev. C. E. Boucher, then Archdeacon of Loughborough, and with the end of the war he settled in Wetherby, where he lived and worked for the rest of his life.

R. W. L. writes: There is no doubt that the effect of his war service was to undermine Dr. Kitching's health permanently and to make general practice a hard thing. He was interested in ophthalmology and for many years acted as assistant in the out-patient department of Harrogate General Hospital, a position he had to leave at the start of the National Health Service. In later years he occupied an important position in the organization of the British Empire Cancer Campaign in Yorkshire. Kitching was not a man of many words, and speeches did not come easily from him. His favourite medium was the pen, and his articles in and contributions to the correspondence columns of many serious publications appeared in a steady stream, on all subjects from foreign policy to euthanasia. Mostly, of course, they were on or about medical matters, and especially the National Health Service, and, whether one agreed or not with his conclusions, they had a force and pungency which compelled attention and drew upon him a great deal of comment from many distinguished people in the literary world. His colleagues head the list of a large number of Yorkshire folk who will miss him very much and who extend their sympathy to his widow and family.

C. K. D. EDWARDS, E.D., M.B., Ch.B.

Dr. C. K. D. Edwards, who was for many years in practice at Ainsdale, Southport, died at his home at Lustleigh, near Newton Abbot, Devon, on March 13. He was 60 years of age.

Born in Liverpool on January 2, 1899, Cyril Kent Dodwell Edwards was the son of Dr. Percy Edwards, and was educated at Liverpool College. He was commissioned in the Royal Artillery in 1918 for service in the first world war, and, after demobilization, studied medicine at Liverpool University, where he graduated M.B., Ch.B. in 1923. He went into practice at Ainsdale in the following year, and was honorary secretary of the Southport Division of the British Medical Association from 1931 to 1937. As a Territorial officer he was called up in August, 1939, and went to France with No. 127 Field Ambulance. He had a very hard time during the retreat to Dunkirk, being in continuous action, and was one of the last R.A.M.C. officers to leave Dunkirk on June 1, 1940. Promotion followed, and he went to France again as A.D.M.S., 79th Armoured Division, with the rank of acting colonel. After the war he continued to serve in the Territorial Army and became A.D.M.S., Southern Command A.A., R.A., and for his long services was awarded the Efficiency Decoration in 1949. In 1955 he was appointed an Officer of the Venerable Order of St. John of Jerusalem.

He retired from practice in 1950 and went to live at Lustleigh, becoming chairman of the Ministry of Labour and National Service medical board in Exeter. Always an idealist and unsparing of himself, he soon became associated with many local activities. He was chairman of the parish council and president of the Lustleigh Horticultural Society and of the Newton Abbot division of the St. John Ambulance Brigade. He was interested in heraldry and history, and just before his last illness had written and published a guide to Lustleigh. In the last few years his health had not been good, but his many friends had been happy to see a big improvement during the winter, so that the news of his serious illness from a coronary thrombosis came as a shock. In 1937 he married Miss Hilary Frances Charlton, and to her we offer our deepest sympathy.—E. L. R.

E. D. RUTHERFORD, M.B., B.Ch.

Surgeon Captain E. D. Rutherford, R.N. (ret.), died at Newcastle, Co. Down, Northern Ireland, on March 7, at the age of 81.

The son of Dr. Robert A. Rutherford, J.P., who practised at Manorhamilton, Co. Leitrim, for over fifty years, Ernest Davis Rutherford was born on August 16, 1877, and was educated at Portora Royal School, Enniskillen. He studied medicine at the former Queen's College, Belfast, and graduated M.B., B.Ch. in the Royal University of Ireland in 1902. After doing a few trips as surgeon in the Bibby Line, as well as holding some posts as a locumtenent, he entered the Royal Navy as surgeon lieutenant in 1904, and in the next few years served at Haslar Hospital, in Malta, and in the Far East. His service in the first world war included some pioneer work on asdic equipment, and in 1918 he was decorated by the King of the Hellenes with the Order of the Redeemer for his services to Greek civilians. He retired from the Navy in 1922. He then took a postgraduate course at St. Thomas's Hospital, London, in electrotherapy, which he later practised in Belfast, holding an honorary appointment in that specialty at the Royal Victoria Hospital.

On the outbreak of the second world war in 1939 he was recalled to the Royal Navy to hold shore appointments, serving at first at the Admiralty and subsequently in H.M.S. *Excalibur*, at Alsager. He retired at the end of 1944. He leaves a widow and one son.

Medical Notes in Parliament

MENTAL HEALTH BILL

The provisions in the Mental Health Bill for the compulsory admission to hospital or guardianship of patients convicted of criminal offences are being closely examined by the House of Commons standing committee. One of the issues, discussed at their meeting on March 19, is whether the power given to the Home Secretary to impose special restrictions on discharge is in conflict with the new conception of treatment for mental disorder.

Restrictions after Court Conviction

Clause 64 states that where a hospital order is made in respect of an offender by a court of assize or quarter sessions, and it appears to the court, having regard to the nature of the offence, the antecedents of the offender, and the risk of his committing further offences, that it is necessary for the protection of the public so to do, the court may order that the offender shall be subject to special restrictions, either without limit of time or during a specified period. Subsection (3) (c) declares that where a restricted discharge order has been made the power to grant leave of absence, transfer, and discharge shall be exercisable only with the consent of the Secretary of State.

Mr. KENNETH ROBINSON (St. Pancras North, Lab.) moved to delete the provisions for restricted discharge and the related authority of the Home Secretary. He argued that they confused the function of the hospital with the function of the penal institution; and that one of the main purposes of the Royal Commission and of the Bill was to change the mental hospital from a custodial institution into a genuine hospital. What was the purpose of placing a fixed period on the length of treatment unless some element of penal sanction was involved? Even though the court had the benefit of some medical recommendation that the patient or offender required treatment, that doctor certainly could not say how long treatment was likely to be necessary. The basis of the amendments was his belief that the decision when a patient's treatment was completed or when treatment could no longer be of any value should be a medical decision, and not that of the Home Secretary. He quoted what the B.M.A. had said about subsection (3):

> "As the Bill stands, a person detained in hospital in pursuance of an order made by the court, can only be released with the consent of the Home Secretary. This may lead to the situation that a person may continue to be detained in hospital, when in the opinion of the responsible medical officer, he has either recovered or is no longer responsive to medical treatment. The Committee [the Psychological Medicine Group Committee] considers that it is no part of the functions of a hospital to be a place of detention where criminal or legal issues only are involved, and where medical grounds no longer exist."

and added that the same misgivings had been expressed by the Association of Psychiatric Social Workers and the National Association for Mental Health, and that the Society of Mental Welfare Officers was also anxious about it. It was true that the Royal Commission had given this procedure a reluctant blessing, but it seemed to him strongly implicit in their report that they only intended that it should be used in respect of psychopathic patients.

Dr. DONALD JOHNSON (Carlisle, Con.) thought it was probably necessary for some provision of this kind to be in the Bill. He was not so certain that patients would get out sooner if they were left to medical recommendations. His experience would incline him to back the Home Secretary, because doctors were, understandably, very nervous about this type of case and the possible criticism if patients were let out too soon.

"A Fairly Narrow Class of Patients"

Mr. D. RENTON, Under Secretary, Home Office, pointed out that they were dealing with a fairly narrow class of patients, people who had already been convicted and for whom the court had already decided that ordinary forms of treatment within the penal system were not appropriate. The court had the power, for reasons of public security, to say that a person should not be discharged, either at all or for whatever the period might be, unless the Home Secretary said it was all right from the point of view of public security. He recited the views expressed by the Royal Commission in paragraphs 518 and 520. The power of conditional discharge would be a useful method of meeting the difficult cases where there was a conflict between the hopes of the medical people that a man guilty of violent assaults was now mentally well and the duty of the Home Secretary to protect the public.

There were also other cases in which the Home Secretary might think it desirable to ask the medical people to think a little longer before giving an absolute discharge. The first example of cases in which the power might be exercised was the person charged with murder but convicted of manslaughter on the ground of diminished responsibility. There was the case with a history of recurrent mental illness and of offences against the person when the person's mental condition had relapsed. There was the subnormal person who persistently committed sexual offences against children. There was the adult psychopath with a history of violence. In all these cases the question of protecting the public must arise, and considerations other than medical considerations ought to be taken into account.

Amendments Negatived

These arguments did not convince Mr. SOMERVILLE HASTINGS (Barking, Lab.). Once it was determined that a crime was the result of mental disease then the patient must be dealt with like any other patient suffering from a disease; otherwise they had failed to appreciate the new conception towards mental illness. He did not agree that danger would be caused to the public. Those who determined the discharge of the patient would have full knowledge of the previous history and of the period in hospital, and would of course be exceedingly careful.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) thought that was an over-simplified view. Most doctors rarely thought in terms other than of curing the patients. They were accustomed to think that any other aspect of a patient's life was somebody else's job. They must have the Secretary of State and the people with the offender's record. It was not the job of the doctor, the psychiatrist, and the hospital to say what was to be his future.

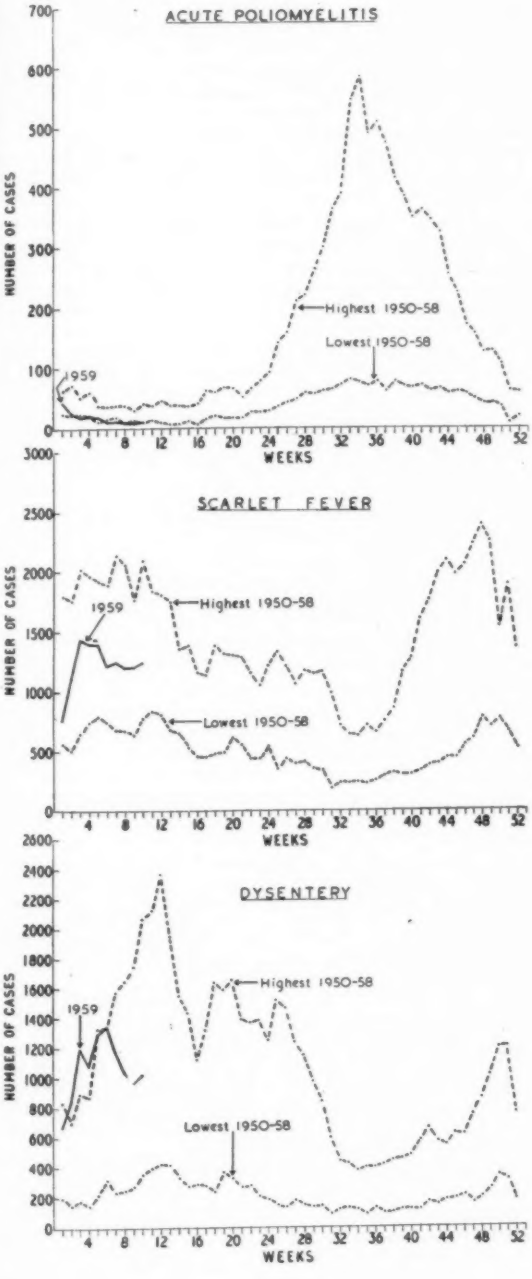
The amendments were negatived.

Mr. ROBINSON had more success with a subsequent proposal. He sought to delete from subsection (3) (b), in order to restore to patients covered by the clause a right of appeal to the mental health review tribunal. Mr. RENTON would not go that far, since he said it would probably frustrate the Home Secretary's power of veto if the tribunal had a parallel power of discharge; but he gave an undertaking to discuss with the Minister of Health the possibility of giving patients subject to restriction orders the right to initiate consideration by the tribunal itself, with a view to the tribunal tendering advice to the Home Secretary. Mr. ROBINSON accepted this, acknowledging that advice from such a body would not be lightly set aside by a Home Secretary, and withdrew his own amendment.

Vital Statistics

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus - - - - - -, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



Smallpox at Liverpool

No further cases of smallpox had been reported at Liverpool by the time of going to press on March 31. The first case to be reported (*Journal*, March 14, p. 731) was a 21-year-old medical student. He had mild but typical smallpox, from which recovery was rapid. The second case, in a hospital technician (*Journal*, March 28, p. 869), was of a much-modified attack in a well-vaccinated subject. We are indebted to Professor A. B. SEMPLE for the following details: Though the diagnosis was not confirmed in the laboratory, the clinical appearances were typical of smallpox which did not get beyond the prodromal stage. In addition to backache and rise of temperature the patient developed a rose-morbilliform rash, which then faded. The source of the outbreak remains unknown.

Week Ending March 14

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available:

	Week Ending Mar. 7	Mar. 14
Measles		
London	1,360	**1,485**
Lambeth	118	**158**
Lewisham	99	**139**
Surrey	1,317	**1,458**
Croydon C.B.	123	**235**
Sussex	710	**845**
Brighton C.B.	122	**105**
Hampshire	705	**713**
Portsmouth C.B.	68	**109**
Southampton C.B.	147	**121**
Essex	2,286	**1,919**
Dagenham M.B.	141	**185**
Basildon C.B.	106	**199**
Gloucestershire	541	**459**
Bristol C.B.	162	**166**
Staffordshire	743	**887**
Stoke on Trent C.B.	180	**215**
Warwickshire	1,337	**1,260**
Birmingham C.B.	582	**531**
Coventry C.B.	347	**297**
Lancashire	1,887	**1,494**
Liverpool C.B.	165	**103**
Manchester C.B.	315	**268**
Devonshire	236	**265**
Plymouth C.B.	45	**135**
Acute Poliomyelitis		
Yorkshire West Riding	1	**3**
Leeds C.B.	**0**	**2**
Wiltshire	**0**	**2**
Marlborough and Ramsbury R.D.	**0**	**2**
Lancashire	2	**2**
Manchester C.B.	**0**	**1**
Stretford M.B.	**0**	**1**
Paratyphoid Fever		
Gloucestershire	1	**3**
Bristol C.B.	1	**3**
Kent	**0**	**1**
Sittingbourne and Milton	**0**	**1**
Lancashire	**0**	**1**
Preston C.B.	**0**	**1**
Dysentery		
Lincolnshire	118	**134**
Grimsby C.B.	49	**62**
Cleethorpes M.B.	12	**20**
Middlesex	49	**83**
Tottenham M.B.	3	**35**
Warwickshire	71	**84**
Coventry C.B.	47	**62**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 14** (No. 10) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	5	0	3	0		1	0	1	0	4
Dysentery	1,027	86	136	8	10	1,068	135	215	7	4
Encephalitis, acute	2	0		0		4	0		0	
Enteric fever:										
Typhoid	0	0	1	0	1	0	0	0	0	1
Paratyphoid	5	0	1 (B)	0		6	0	0	0	35 (B)
Food-poisoning	126	27	4	1		149	21	26	0	
Infective enteritis or diarrhoea under 2 years				7	16				17	25
Measles*	22,733	1485	967	612	863	4,532	210	95	33	56
Meningococcal infection	28	2	8	1	1	24	2	6	0	1
Ophthalmia neonatorum	32	3	5	0		40	2	3	0	
Pneumonia†	2,039	100	535	29	33	690	46	355	16	4
Poliomyelitis, acute:										
Paralytic	11	0	3	0		5	0	2	0	3
Non-paralytic	1	0	0			5	0			
Puerperal fever§	282	45	9	0		199	34	16	1	
Scarlet fever	1,240	63	47	27	18	938	53	101	28	32
Tuberculosis:										
Respiratory	637	52	88	11		591	104	87	16	
Non-respiratory	46	2	14	1		78	7	12	3	
Whooping-cough	585	21	59	51	113	620	38	48	3	16

DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	3	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	0	1	0	0	1	0	0	0	0
Influenza	907	35	29		8	76	1	1	0	0
Measles		0	2	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	1,384	115	55	27	21	722	64	37	14	
Poliomyelitis, acute	1	1		0	0	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	121	11	7	1	7	102	13	11	4	2
Non-respiratory		0	1	0	1		2	0	0	1
Whooping-cough	1	0	0	0	1	0	0	0	0	0
Deaths 0–1 year	340	19	34	8	26	343	39	17	8	14
Deaths (excluding stillbirths)	13,560	1061	737	164	256	11,590	929	638	142	183
LIVE BIRTHS	15,826	1410	1033	272	395	15,832	1343	1038	223	356
STILLBIRTHS	328	29	22			367	39	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

World Health Day.—This year W.H.O. has designated April 7 as World Health Day, choosing as its theme "Mental Illness and Mental Health To-day." The purpose of the day is to encourage public interest in one of the great current health problems.

B.M.A.–C.M.A. Art Exhibition.—The closing date for entries to the art exhibition which will be held in Edinburgh during the Combined Annual Meeting of the British and Canadian Medical Associations has been advanced to April 30. Those who wish to exhibit are invited to get in touch with Professor B. G. MAEGRAITH, School of Tropical Medicine, University of Liverpool, Pembroke Place, Liverpool, 3; Dr. A. M. RACKOW, 11, Deepdale, Parkside Avenue, Wimbledon, London, S.W.19; or Professor D. E. C. MEKIE, Royal College of Surgeons, 18, Nicolson Street, Edinburgh, 8. A competition will be held in connexion with the exhibition, and Messrs. E. and S. Livingstone, the Edinburgh publishers, have presented a trophy. The competition will be judged by EARL HAIG OF BEMERSYDE and Mr. R. LYON, principal of the Edinburgh College of Art.

Edinburgh Chair of Medical Chemistry.—Dr. R. B. FISHER, D.Phil., is to succeed Professor G. F. MARRIAN, F.R.S., when the latter retires from the Chair of Chemistry in relation to Medicine at Edinburgh University on September 30. Dr. Fisher is at present demonstrator in biochemistry at Oxford.

Dr. Fisher was born in 1907. He entered Oxford in 1926 with an open scholarship in chemistry and physics to St. John's College. Three years later he graduated with first-class honours in physiology. From 1929 to 1933 he was Christopher Welch scholar in biology, subsequently proceeding B.Sc. and D.Phil. In 1935 he was appointed university demonstrator in biochemistry at Oxford, and in 1945 became a lecturer of Wadham College. In 1939 he was awarded a Rockefeller travelling fellowship, but was unable to take this owing to the outbreak of war. During the war Dr. Fisher collaborated with Sir Solly Zuckerman, F.R.S., in studies on the effects of blast from high explosives, later becoming director of a specialized operational research unit of the Air Ministry. In 1945 he acted as a consultant in Japan to the U.S. War Department. In 1954 Dr. Fisher published his book on protein metabolism.

Glasgow University.—Appointments to the Chairs of Orthopaedics and of Infectious Diseases were announced by the Court of Glasgow University on March 27. Mr. ROLAND BARNES, the present university reader in orthopaedics, has been appointed to the Chair of Orthopaedics; and Dr. THOMAS ANDERSON, university reader in infectious diseases, has been appointed to the Chair of Infectious Diseases.

Mr. Barnes graduated at Manchester University B.Sc. in 1927 and M.B. in 1930, obtaining the F.R.C.S. in 1933. In 1947 he was elected F.R.F.P.S. After appointments at the Manchester Royal Infirmary he became, in 1939, director of the E.M.S. orthopaedic centre at Winwick, Lancs. In 1943 he joined the staff of Glasgow University, taking charge of the orthopaedic department at the Western Infirmary.

Dr. Anderson graduated in medicine at Glasgow University in 1928, proceeding to the M.D. with honours and the Bellahouston gold medal in 1945. In 1940 he was elected F.R.C.P.Ed. and in 1947 F.R.F.P.S. After holding various medical posts in Glasgow, Dr. Anderson was appointed in 1946 visiting physician of Knightswood Hospital and consultant in infectious diseases and university lecturer in that subject. In 1951 he took charge of the department of infectious diseases at Ruchill Hospital and became university reader in infectious diseases.

Royal College of Surgeons.—An appeal for £3m. to support the College's programme of teaching, research, and rebuilding was launched on March 24 by its president, Sir JAMES PATERSON ROSS. The appeal followed the *première*, at the College, of the film *Life in Emergency Ward 10*, to

which an audience of leading industrialists and surgeons had been invited. During the evening it was announced that £937,000 had already been received. (*The Times*, March 25.)

Blood Club, Birmingham.—A Blood Club has been formed in Birmingham. Its aim is the informal discussion of problems of haematology and blood transfusion, and membership is open to all interested in this field; pathologists, physicians, paediatricians, obstetricians, surgeons, and anaesthetists will be welcome. Meetings will take place on Friday evenings at 6 p.m. at three-monthly intervals. So far two meetings have been held in the Department of Experimental Pathology. Further information may be obtained from Dr. ELIZABETH TOPLEY, c/o Blood Transfusion Service, 15, Ampton Road, Edgbaston, Birmingham, 15.

Wessex Regional Hospital Board.—The new board held its first meeting on March 16. Dr. J. REVANS, deputy S.A.M.O. to the south-west metropolitan board, was appointed as the board's senior medical administrative officer.

Sir Stewart Duke-Elder has been awarded the Charles Mickle Fellowship for 1959 by the Senate of the University of Toronto. The award is for "the member of the medical profession who has done most during the preceding ten years to advance sound knowledge of a practical kind in medical art or science."

University of St. Andrews.—On June 30 the degree of Doctor of Laws at the University will be conferred on Sir GEORGE LINDOR BROWN, F.R.S., Jodrell Professor of Physiology, University College London, secretary and Vice-president of the Royal Society; and on Professor D. R. DOW, Emeritus Professor of Anatomy, St. Andrews University.

B.M.J. Index.—The half-yearly indexes to Volume II of the *Journal* and the *Supplement* for 1958 are now being sent to members who receive them regularly and to subscribers. Members who have not previously asked for the indexes to be sent regularly to them can obtain copies, post free, on application to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1; those wishing to receive the indexes regularly should mention this.

COMING EVENTS

Auxiliary Royal Army Medical Corps Funds.—The annual general meeting will be held at 5 p.m., April 6, at 11, Chandos Street, London, W.1.

Tudor Edwards Lecture.—Sir CLEMENT PRICE THOMAS will lecture on "Conservative and Extensive Resection for Carcinoma of the Lung" on April 8 at 5 p.m. at the Royal College of Surgeons of England.

Lumleian Lectures.—Professor E. J. WAYNE will lecture on "Clinical and Metabolic Studies in Thyroid Disease" on April 14 and 16, at 5 p.m., at the Royal College of Physicians, Pall Mall East.

The Association of Clinical Pathologists. — The 62nd general meeting will take place in the Medical School, University of Manchester, on April 16, 17, and 18. Further details from Professor J. N. CUMINGS, Department of Chemical Pathology, The National Hospital, Queen Square, London, W.C.1.

British Association of Physical Medicine.—The annual meeting will be held on April 17 and 18 at Guy's Hospital, London, S.E.1. Details from the association, 47, Lincoln's Inn Fields, London, W.C.2.

Institute of Diseases of the Chest.—Clinical demonstrations, open to medical practitioners without fee, will be held at the Institute (in the grounds of the Brompton Hospital, Fulham Road, London, S.W.3) on Fridays at 5 p.m. from April 17 to July 3.

Wessex Rahere Club.—Spring dinner at the Royal Clarence Hotel, Exeter, on April 18. Details from Mr. A. D. BATEMAN, F.R.C.S., 11, The Circus, Bath.

British Tuberculosis Association.—The provincial meeting in collaboration with the Thoracic Society of Wales will be held in Cardiff on April 17 and 18. All lectures will be held in the Department of Pathology, Cardiff Royal Infirmary. Further details from the Administrative Secretary, The British Tuberculosis Association, 59, Portland Place, London, W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, April 4

SOUTH-WEST CHEST SOCIETY.—At Library, Royal Devon and Exeter Hospital, 2.15 to 5.15 p.m., papers by Dr. D. A. Williams, Dr. Kenneth Citron, and Dr. I. G. Kreeger.

Monday, April 6

MARLBOROUGH DAY HOSPITAL.—8.15 p.m., Dr. Peter D. Scott: Treatment of Sex Perversions.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. Rodney Smith: Tumours of the Liver; 6.30 p.m., Mr. D. Patey: Infection of the Salivary Glands.

Tuesday, April 7

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. Rodney Maingot: Repair of Large Incisional and Inguinal Herniae; 6.30 p.m., Mr. Stephen J. H. Miller: Exophthalmos and its Complications.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. J. N. Milnes: Neurology.

Wednesday, April 8

MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., valedictory address by Dr. H. W. Donovan: General Practice: Its Place and Prospect.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Tudor Edwards Lecture by Sir Clement Price Thomas: Conservative and Extensive Resection for Carcinoma of the Lung.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. C. E. Drew: Pulmonary Resection for Metastases; 6.30 p.m., Mr. R. Vaughan Hudson: Thyroiditis.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mr. R. J. Wallis, M.A.: Laminated Plastics in Everyday Hygiene (illustrated).

Thursday, April 9

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Dr. Ludwig Guttmann: Modern Trends in the Treatment and Rehabilitation of Traumatic Paraplegics, followed by silent film.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor T. J. S. Patterson: Congenital Deformities of the Hand.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—6.15 p.m., Sir Stanford Cade: Malignant Melanoma.

ROYAL EYE HOSPITAL.—5.30 p.m., Dr. T. H. Whittington: Aspects of Refraction Work—(2) The Reduced Eye, and Retinoscopy.

Friday, April 10

INSTITUTION OF ELECTRICAL ENGINEERS: MEDICAL ELECTRONICS DISCUSSION GROUP.—5.30 for 6 p.m., discussions—Professor E. C. Cherry: Problems of Sight, Hearing, and Touch. Mr. H. C. W. Stockbridge: Human Engineering Recording Problems.

MEDICAL RESEARCH COUNCIL.—At National Institute for Medical Research, Mill Hill, N.W., 5 p.m., Dr. S. E. Luria (Massachusetts): Mechanisms of Infective Heredity in Bacteria.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. J. B. Oldham: Complications of Abdominal Operations; 6.30 p.m., Dr. H. A. Sissons: Primary Tumours of Bone.

Saturday, April 11

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Addenbrooke's Hospital, Symposium on Paediatrics. 10.15 a.m., Dr. Arthur Rook: The Child with Eczema; 11 a.m., subject: Mentally Retarded Child. Papers by Dr. Douglas Gairdner, Dr. Janet Roscoe, Dr. D. R. Davis, Dr. R. E. Glennie, and Mr. W. F. H. Stubbings. 3.45 p.m., Dr. C. D. Farris: Current Problems in the Treatment of Dental Conditions in Children.

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Farnborough Hospital (Children's Department), 3 p.m., clinical meeting. Members of Bromley Division (B.M.A.) are invited.

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Joyce Green Hospital, Dartford, 10.30 for 11 a.m., Dr. Paul Forgacs: Some Clinical Applications of Respiratory Physiology; Dr. John Bullough: Resuscitation in Chronic Bronchitis; Demonstration of Respirators and Methods of Physiological Measurement.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Barrow.—On March 14, 1959, at B.M.H., Imtarfa, Malta, G.C., to Maureen (formerly O'Callaghan) and Squadron Leader B. A. J. Barrow, M.B., R.A.F., Episkopi, Cyprus, a sister for Paul and Claire—Siobhan Elizabeth.

Earnshaw.—On March 1, 1959, to Gillian (formerly Cook), M.B., B.Chir., wife of Tony Earnshaw, M.B., B.Chir., of Earl Shilton, Leicester, a second son—Timothy David.

Lockett.—On March 20, 1959, to Gillian, wife of Dr. Harry Lockett, of Reading, Berks, a sister for Stephen and Felicity.

DEATHS

Bisset.—On March 23, 1959, Alexander Andrew Bisset, M.D., of 16, Victoria Avenue, Harrogate, Yorks, aged 72.

Broadhurst.—On March 22, 1959, at 58a, Harvard Road, Chiswick, London, W., Harry Cecil Broadhurst, M.B., B.S., aged 67.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Aetiology of Leukaemia

Q.—*Why is leukaemia said to be cancerous?*

A.—Willis[1] defined a tumour as "an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change." Human leukaemias are characterized by an excess of leucocyte-forming tissue which bears no relation to the bodily demands for leucocytes. The excessive proliferation occurs not only in the normal sites of leucocyte production, but also in other tissues, which may be infiltrated or ulcerated by the leukaemic cells. The leukaemic cells are not normal leucocytes. Even when they appear morphologically normal, as in many cases of chronic granulocytic leukaemia, histochemical tests show that they lack enzymes such as alkaline phosphatase. In chronic lymphocytic leukaemia the lymphocytes almost always show some morphological abnormalities, and this is true also of all forms of acute leukaemia, when the cells, in addition, fail to differentiate normally. In the case of lymphocytic leukaemia, there is a gradation between typical cases, in which the macroscopic lesions show little tendency to invade surrounding tissues, and those with frankly sarcomatous tumours which invade local structures and spread to distant parts by way of the lymphatics or the blood stream. Many patients with acute leukaemia die from the consequences of haemorrhage or infection before much extramedullary growth and spread has had time to occur. But the use of antimetabolite therapy has prolonged the life of many of these patients, who now live to develop malignant infiltration of the kidneys, skin, or central nervous system, or bulky masses of lymph nodes. If it is accepted that leukaemia has been induced by ionizing radiations,[2] then Willis's final criterion is satisfied, since the leukaemic process continues long after the exposure. The fact that avian leukaemias and some murine leukaemias have proved to be caused by viruses in no way invalidates the contention that leukaemias are malignant growths, for the terms "malignant," "cancerous," "neoplastic," refer only to pathogenesis and not to aetiology.

REFERENCES

[1] Willis, R. A., *The Pathology of Tumours*, 1948, p. 1. Butterworth, London.

[2] Court-Brown, W. M., *Brit. med. Bull.*, 1958, **14**, 168.

Vasoconstricting Nasal Sprays

Q.—*Do nasal sprays containing vasoconstricting agents tend, from their vasoconstrictor action, to prolong the infections they are intended to cure?*

A.—They do not. The object of naso-vasal constriction is not so much to overcome any nasal infection as to reduce the nasal swelling caused by infection and thus allow natural drainage to occur, and in this way the natural defences of the body will overcome the infection. It sometimes happens, however, that certain vasoconstricting agents in the nose have what may be termed a rebound effect—that is to say, after a period of vasoconstriction the nasal mucosa swells up again and the nose becomes even more blocked than it was before. This leads to more frequent use of the vasoconstricting drops until there is almost a permanent nasal obstruction. This should really be regarded as an irritation rather than an infection, and when vasoconstricting nasal drops or a nasal spray are prescribed the patient should be warned of this possibility and asked to report it. If it does happen, then the drops or spray should be stopped.

Interval in Birth of Twins

Q.—*What has been the longest interval between the birth of twins in a case where there has been a single uterus and a single placenta?*

A.—The record interval between twins, to the writer's knowledge, is the 56 days reported in a case by Williams and Cummings,[1] but this was a case of a double uterus each with its own cervix. For a single uterus an interval of hours is not rare and one of days has been recorded. But as in 85% of all cases of twins the second baby is delivered within 30 minutes of the first, it is now general practice not to allow the interval, even in the absence of other complications such as haemorrhage or foetal distress, to exceed 30–45 minutes. If rupture of the membranes is not in itself followed by the resumption of second-stage contractions, then either a weak pitocin drip is employed or the second baby is extracted. Within this time limit the cervix will not close down on the second foetus, unless ergometrine has inadvertently been given after the birth of the first baby, in which case general anaesthesia will permit the extraction of the second baby.

REFERENCE

[1] Williams, B., and Cummings, G., *J. Obstet. Gynaec. Brit. Emp.*, 1953, **60**, 319.

NOTES AND COMMENTS

Migraine in Pregnancy.—Dr. E. B. FRENCH (Edinburgh) writes: Ergotamine is in the news judging from your issue of March 7. I have in my wards at the present time a woman aged 45 who is about to lose both legs below the knee and the forefinger and thumb of the right hand. This disaster follows taking a proprietary tablet containing 1 mg. (since confirmed by analysis) of ergotamine tartrate three times a day to a total of seven tablets, given for menorrhagia as advised by the makers and in the dosage which they suggest. On the day she took the last tablet no arm pulse was palpable distal to the subclavians and no leg pulse below the thready femorals. Bounding carotid pulses and an unusually loud aortic second sound were the only evidence that the aortic blood pressure was well maintained. It is doubtful whether capillary constriction suggested in an answer in "Any Questions?" (March 7, p. 662) is ever the cause of gangrene. It is clear that in this case at least there was a shut-down of major arteries. One week later the temporal, popliteal, radial, and most finger pulses had returned.

OUR EXPERT replies: The case recorded by Dr. French fully confirms the warning which was given about the use of ergotamine. In those persons who are sensitive its use has produced nothing less than disaster. Whenever a new case is reported it becomes a matter for astonishment that responsible manufacturers make it for medical use. Capillary *constriction* was not mentioned in the answer which was given. Whether the effect on the capillary circulation is primary, or secondary to an effect on arteries, is surely not an important point.

Corrections.—In the article on "Myasthenia Gravis" by J. W. Aldren Turner (March 21, page 778), tetraethylpyrophosphate was abbreviated erroneously to T.E.P.T. instead of T.E.P.P.

We regret that it was incorrectly announced in our Medical News columns of March 28 that Sir George Lindor Brown, F.R.S., was emeritus professor of anatomy at the University of St. Andrews. An amended announcement is made in this week's Medical News.

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